```
=> fil lreg
FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005
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LREGISTRY IS A STATIC LEARNING FILE

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=> fil reg
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provided by InfoChem.

STRUCTURE FILE UPDATES:   10 OCT 2005  HIGHEST RN 864908-12-3
DICTIONARY FILE UPDATES:  10 OCT 2005  HIGHEST RN 864908-12-3

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> fil zcap
FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005
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FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

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=> fil hcap
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FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

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=> fil uspatfull
FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 6 Oct 2005 (20051006/PD)
FILE LAST UPDATED: 6 Oct 2005 (20051006/ED)
HIGHEST GRANTED PATENT NUMBER: US6952836
HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461
CA INDEXING IS CURRENT THROUGH 6 Oct 2005 (20051006/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 6 Oct 2005 (20051006/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<

>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil uspat2
FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 2001 TO PUBLICATION DATE: 11 Oct 2005 (20051011/PD)
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)
HIGHEST GRANTED PATENT NUMBER: US2005054189
HIGHEST APPLICATION PUBLICATION NUMBER: US2005222704
CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

=> fil toxcenter
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TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and

http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

=> fil beilstein
FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005

FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON JUNE 29, 2005

FILE COVERS 1771 TO 2005.
*** FILE CONTAINS 9,271,550 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****

NEW

*** PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**
*** NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

=> fil chemcats
FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005

FILE LAST UPDATED 08 OCTOBER 2005 (20051008/UP)

For details on recent updates in CHEMCATS, enter NEWS FILE at an arrow prompt. For the list of suppliers currently in the file, enter HELP SPA, HELP SPBC, HELP SPDH, HELP SPIN, HELP SPOP, and HELP SPQZ. For the list of current catalogs, enter HELP CTA, HELP CTBC, HELP CTDH, HELP CTIN, HELP CTOP, and HELP CTQZ.

This database is provided on an "as is" basis. Please consult the suppliers for current information regarding pricing, regional availability, available quantities, purities, etc. THERE ARE NO

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=> file stnguide
FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

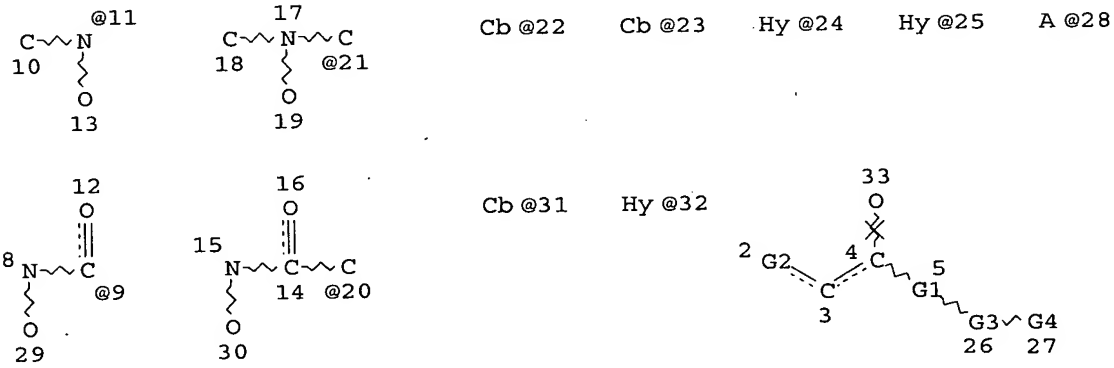
=> d his l59

(FILE 'REGISTRY' ENTERED AT 15:30:49 ON 11 OCT 2005)

FILE 'STNGUIDE' ENTERED AT 15:31:00 ON 11 OCT 2005

FILE 'REGISTRY' ENTERED AT 15:35:36 ON 11 OCT 2005
L59 57 S L57 FUL

=> d que stat l59
L57 STR



VAR G1=22/23/24/25
VAR G2=9/11/20/21
REP G3=(2-20) 28
VAR G4=31/32
NODE ATTRIBUTES:
NSPEC IS RC AT 3
NSPEC IS RC AT 4
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 28
NSPEC IS RC AT 33
CONNECT IS E2 RC AT 8
CONNECT IS E1 RC AT 13
CONNECT IS E2 RC AT 15
CONNECT IS E1 RC AT 19
CONNECT IS M2 RC AT 22
CONNECT IS M2 RC AT 23

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CONNECT IS M2  RC AT  24
CONNECT IS M2  RC AT  25
DEFAULT MLEVEL IS ATOM
GGCAT   IS MCY  UNS  AT  22
GGCAT   IS PCY  UNS  AT  23
GGCAT   IS MCY  UNS  AT  24
GGCAT   IS MCY  UNS  AT  25
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E6 C  AT  22
ECOUNT  IS E10 C  AT  23
ECOUNT  IS E5 C  E1 N  AT  24
ECOUNT  IS E4 C  E2 N  AT  25
ECOUNT  IS M3-X13 C  AT  31
ECOUNT  IS M1-X13 C  AT  32

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
L59           57 SEA FILE=REGISTRY SSS FUL L57

100.0% PROCESSED   65451 ITERATIONS                    57 ANSWERS
SEARCH TIME: 00.00.01


=> d his l66

     (FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS'
     ENTERED AT 16:23:16 ON 11 OCT 2005)
L66           26 DUP REM L65 (8 DUPLICATES REMOVED)
                 SAVE TEMP L66 HOF197MULS1/A

     FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005

     FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005

     FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005

     FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005

     FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005

     FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005

     FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005

=> d que nos l66
L57             STR
```

```
L59           57 SEA FILE=REGISTRY SSS FUL L57
L65           34 SEA L59
L66           26 DUP REM L65 (8 DUPLICATES REMOVED)


=> d l64
L64           ANALYZE L59 1- LC :        7 TERMS

TERM #    # OCC   # DOC   % DOC LC
------ ------- ------ ------ ---------------
     1       56     56  98.25 CA
     2       56     56  98.25 CAPLUS
     3       52     52  91.23 USPATFULL
     4       46     46  80.70 TOXCENTER
     5        1      1   1.75 BEILSTEIN
     6        1      1   1.75 CHEMCATS
     7        1      1   1.75 USPAT2
*********  END OF L64***


=> d ibib ed ab hitstr ind l66 1-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y


NO VALID FORMATS ENTERED FOR FILE 'CHEMCATS'
In a multifile environment, each file must have at least one valid
format requested.  Refer to file specific help messages or the
STNGUIDE file for information on formats available in individual
files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):end

=> d l66 ibib ed ab ind hitstr retable 1-10
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y


L66  ANSWER 1 OF 26  HCAPLUS  COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:120672  HCAPLUS
DOCUMENT NUMBER:          140:177322
TITLE:                    Hydroxamic acid derivative inhibitors of matrix
                          metalloproteinases and/or TNFα converting enzyme
                          for use in treatment of diseases
INVENTOR(S):              Maduskuie, Thomas P.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 81 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    -------------------      --------
     WO 2004012663         A2    20040212    WO 2003-US23989          20030731
     WO 2004012663         A3    20040708
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
```

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004063698 A1 20040401 US 2003-632197 20030731
PRIORITY APPLN. INFO.: US 2002-400237P P 20020801
OTHER SOURCE(S): MARPAT 140:177322
ED Entered STN: 13 Feb 2004
AB MMP or TACE-inhibiting hydroxamic acid derivs. for use in treatment of diseases are disclosed. Thus, 3,N-dihydroxy-2,2-dimethyl-3-[6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I), 4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II), N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpropionamide (IV) as well as 23 other compds. were synthesized and tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's ≤ 10 μM.
IC ICM A61K
CC 7-3 (Enzymes)
Section cross-reference(s): 1
ST hydroxamic acid deriv matrix metalloproteinases inhibitor pharmaceutical; tumor necrosis factor converting enzyme inhibitor hydroxamic acid deriv
IT Inflammation
(Crohn's disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Intestine, disease
(Crohn's; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Arthritis
(Felty's syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Arthritis
(Reiter's syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Granulomatous disease
(Wegener's granulomatosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Inflammation
Reproductive tract, disease
(adnexitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Liver, disease
(alc.-induced; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Lung
(alveolus, hyperoxic injury to; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Antiarteriosclerotics
(antiatherosclerotics; hydroxamic acid derivative inhibitors of matrix

metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Disease, animal
(arthropathy, hydrarthrosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Disease, animal
(arthropathy; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Disease, animal
(asthenia, post-radiation; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Dermatitis
(atopic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Hepatitis
(autoimmune; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Fatigue, biological
(chronic fatigue syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Lung, disease
(chronic obstructive; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Eye, disease
(cornea, ulcer; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Ulcer
(corneal; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Ulcer
(cutaneous, pyoderma gangrenosum; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Joint, anatomical
(disease, hydrarthrosis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Joint, anatomical
(disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Blood coagulation
(disorder; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Heart, disease
(failure; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Muscle, disease
(fibromyalgia; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in

treatment of diseases)
IT Gingiva, disease
Inflammation
(gingivitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Transplant and Transplantation
(graft-vs.-host reaction; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Acute-phase response
Allergy
Allergy inhibitors
Aneurysm
Anorexia
Anti-AIDS agents
Anti-infective agents
Antiarthritics
Antiasthmatics
Antibacterial agents
Antirheumatic agents
Antitumor agents
Asthma
Atherosclerosis
Autoimmune disease
Behcet's syndrome
Cachexia
Cardiovascular system, disease
Dermatitis
Dermatomyositis
Emphysema
Fever and Hyperthermia
Fibrosis
Gout
Hemorrhage
Human
Infection
Inflammation
Lyme disease
Meningitis
Multiple sclerosis
Myasthenia gravis
Neoplasm
Osteoarthritis
Psoriasis
Rheumatic fever
Rheumatoid arthritis
Sarcoidosis
Sepsis
Shock (circulatory collapse)
Sjogren's syndrome
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Human immunodeficiency virus
Mycobacterium
(infection with; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
IT Arthritis
(infectious; hydroxamic acid derivative inhibitors of matrix

metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Reperfusion
(injury, post-ischemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Rheumatoid arthritis
(juvenile; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Eye, disease
(macula, degeneration, age-related; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Glaucoma (disease)
(neovascular; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Inflammation
Periodontium, disease
(periodontitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Bone, disease
Inflammation
(polychondritis, relapsing; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Myositis
(polymyositis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Arthritis
(psoriatic arthritis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Injury
(reperfusion, post-ischemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Connective tissue, disease
(scleroderma; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Inflammation
Spinal column, disease
(spondylitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Brain, disease
(stroke; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Lupus erythematosus
(systemic; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Skin, disease
(ulcer, pyoderma gangrenosum; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Inflammation
Intestine, disease
(ulcerative colitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Eye, disease
Inflammation
(uveitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Blood vessel, disease
Inflammation
(vasculitis; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT Glucocorticoids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(withdrawal syndrome; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT 17031-92-4, Calcium pyrophosphate dihydrate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deposition, disease; hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT 141907-41-7, Matrix metalloproteinase 151769-16-3, Tumor necrosis factor α-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT 96-32-2, Methyl bromoacetate 99-93-4, 1-(4-Hydroxyphenyl)ethanone 100-39-0, Benzyl bromide 103-25-3, 3-Phenylpropionic acid methyl ester 106-41-2, 4-Bromophenol 123-08-0, 4-Hydroxybenzaldehyde 141-78-6, Ethyl acetate, reactions 554-12-1, Methyl propionate 594-19-4, tert-Butyl lithium 598-30-1, sec-Butyl lithium 623-47-2, Ethyl propiolate 886-51-1 1619-62-1, Diethyl dimethylmalonate 2412-80-8, 4-Methylpentanoic acid methyl ester 5111-65-9, 2-Bromo-6-methoxynaphthalene 7150-55-2, 4-Chloro-1-(4-hydroxyphenyl)butan-1-one 15231-91-1, 6-Bromonaphthalen-2-ol 15823-04-8 18162-48-6 28819-26-3 33611-43-7 37493-31-5 57906-98-6 84199-98-4 90610-07-4 119740-95-3 155339-52-9 156002-64-1, (Tetrahydropyran-4-yl)acetic acid methyl ester 162504-75-8 288399-19-9, 4-Chloromethyl-2-methylquinoline 656803-41-7 656803-51-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

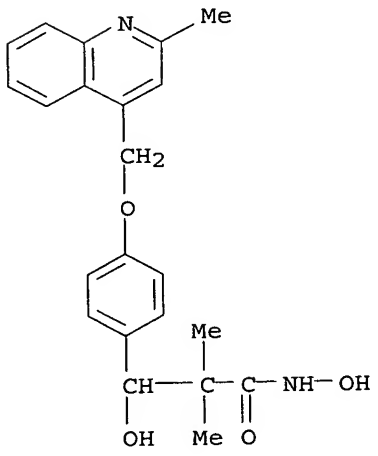
IT 4397-53-9P, 4-Benzyloxybenzaldehyde 6793-92-6P, 1-Bromo-4-benzyloxybenzene 100751-65-3P 656802-94-7P 656802-95-8P 656802-96-9P 656802-97-0P 656802-98-1P 656802-99-2P 656803-00-8P 656803-01-9P 656803-02-0P 656803-03-1P 656803-04-2P 656803-38-2P 656803-40-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

IT **656802-67-4P 656802-68-5P 656802-69-6P 656802-70-9P 656802-71-0P 656802-72-1P 656802-73-2P 656802-74-3P 656802-75-4P 656802-76-5P 656802-77-6P 656802-78-7P 656802-79-8P 656802-80-1P 656802-81-2P**

656802-82-3P 656802-83-4P 656802-84-5P
656802-85-6P 656802-86-7P 656802-87-8P
656802-88-9P 656802-89-0P 656802-90-3P
656802-91-4P 656802-92-5P 656802-93-6P
656803-05-3P 656803-06-4P 656803-07-5P
656803-08-6P 656803-09-7P 656803-11-1P
656803-12-2P 656803-14-4P 656803-16-6P
656803-18-8P 656803-20-2P 656803-22-4P
656803-24-6P 656803-26-8P 656803-28-0P
656803-30-4P 656803-32-6P 656803-33-7P
656803-35-9P 656803-36-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

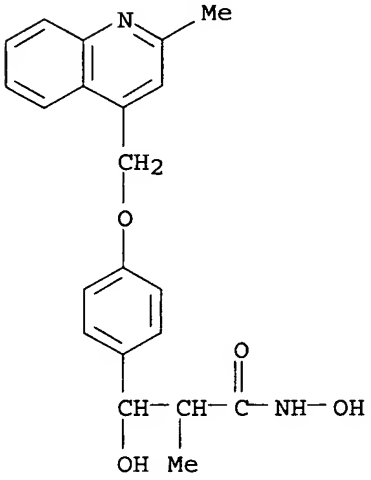
IT 656802-67-4P 656802-68-5P 656802-69-6P
656802-70-9P 656802-71-0P 656802-72-1P
656802-73-2P 656802-74-3P 656802-75-4P
656802-76-5P 656802-77-6P 656802-78-7P
656802-79-8P 656802-80-1P 656802-81-2P
656802-82-3P 656802-83-4P 656802-84-5P
656802-85-6P 656802-86-7P 656802-87-8P
656802-88-9P 656802-89-0P 656802-90-3P
656802-91-4P 656802-92-5P 656803-05-3P
656803-06-4P 656803-07-5P 656803-08-6P
656803-09-7P 656803-11-1P 656803-12-2P
656803-14-4P 656803-16-6P 656803-18-8P
656803-20-2P 656803-22-4P 656803-24-6P
656803-26-8P 656803-28-0P 656803-30-4P
656803-32-6P 656803-33-7P 656803-35-9P
656803-36-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

RN 656802-67-4 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α,α-dimethyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

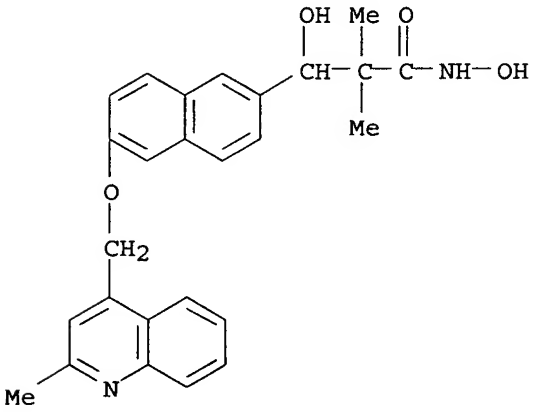


RN 656802-68-5 HCAPLUS

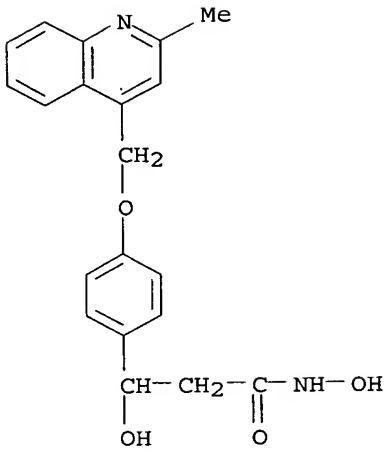
CN Benzenepropanamide, N,β-dihydroxy-α-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



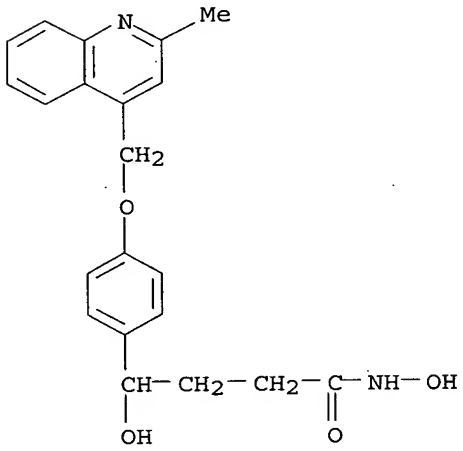
RN 656802-69-6 HCAPLUS
CN 2-Naphthalenepropanamide, N,β-dihydroxy-α,α-dimethyl-6-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



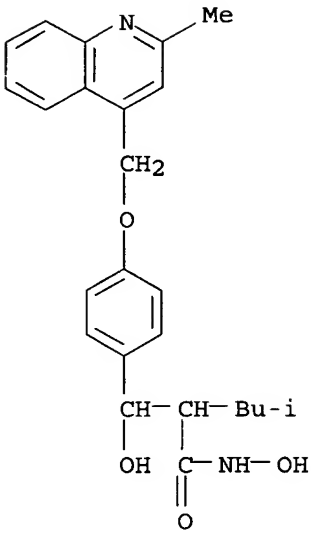
RN 656802-70-9 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



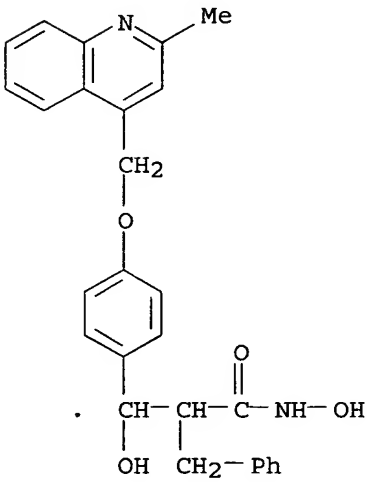
RN 656802-71-0 HCAPLUS
CN Benzenebutanamide, N,γ-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-72-1 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-73-2 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 656802-74-3 HCAPLUS
CN 2-Furanpropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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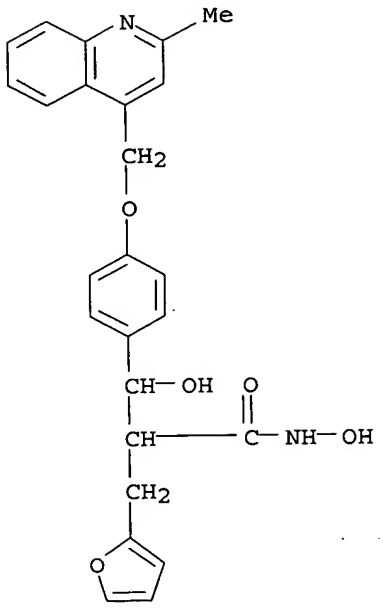

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RN 656802-75-4 HCAPLUS
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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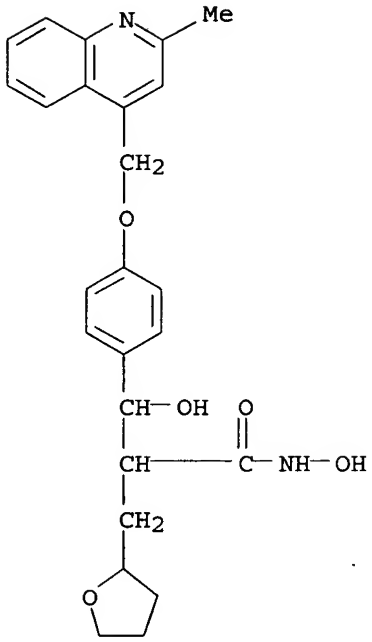

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RN 656802-76-5 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

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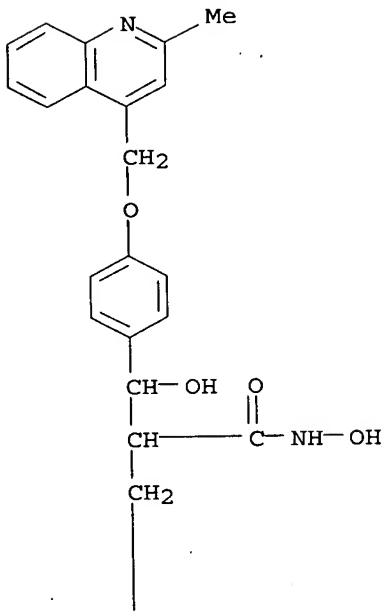

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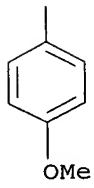

RN 656802-77-6 HCAPLUS
CN Benzenepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)

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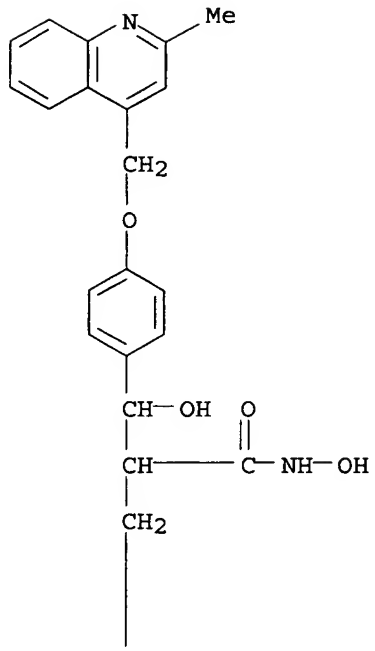

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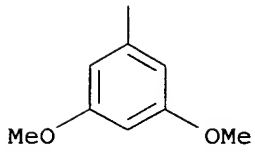
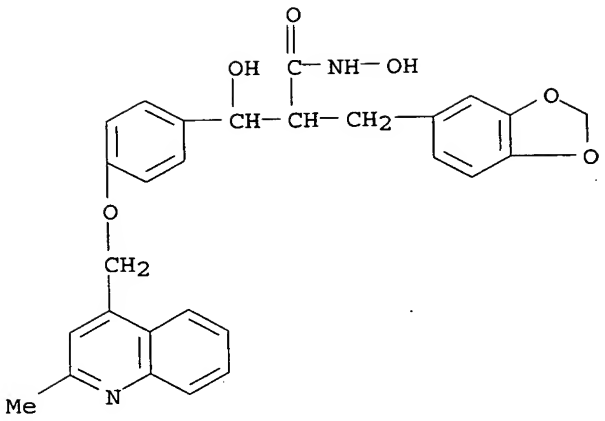
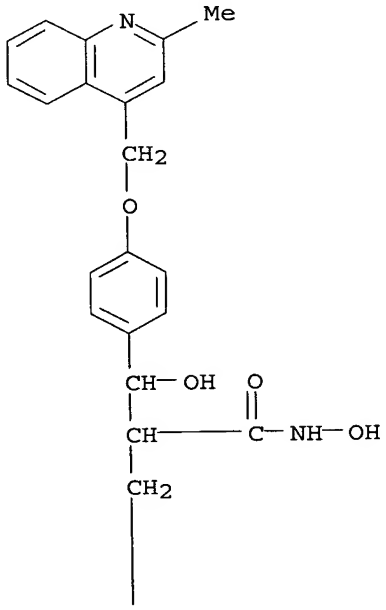


RN 656802-78-7 HCAPLUS
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 656802-79-8 HCAPLUS
CN 4-Pyridinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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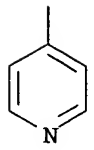
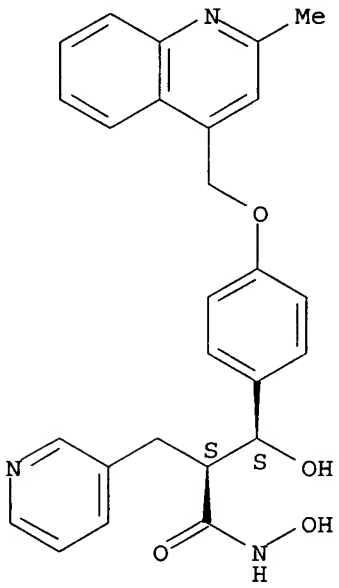


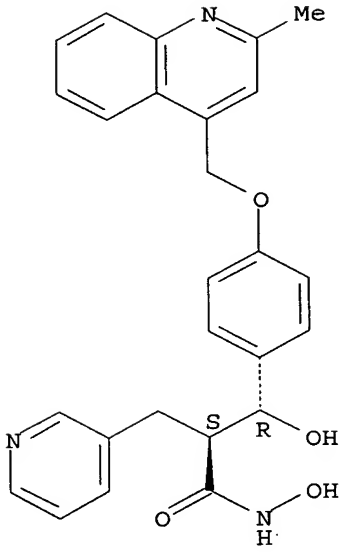
RN 656802-80-1 HCAPLUS
CN 3-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



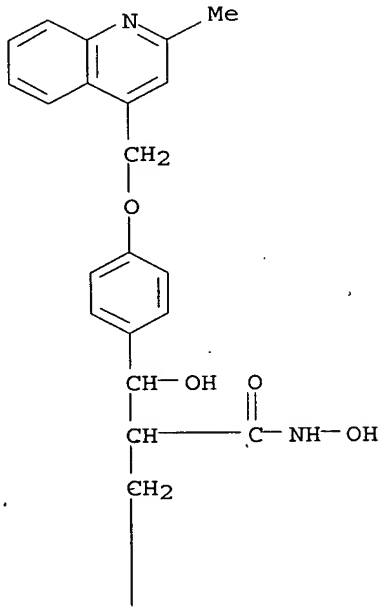
RN 656802-81-2 HCAPLUS
CN 3-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656802-82-3 HCAPLUS
CN 4-Morpholinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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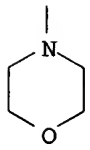

RN 656802-83-4 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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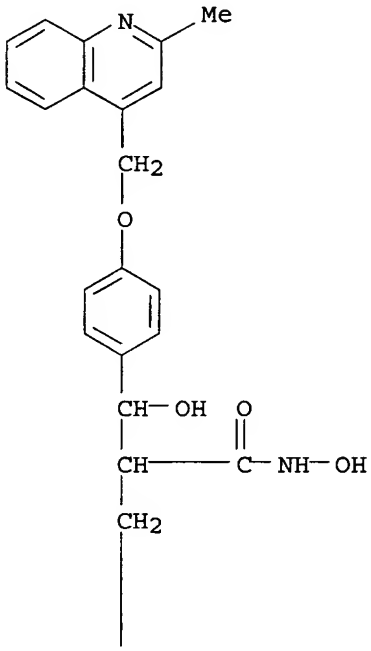

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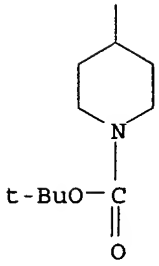

RN 656802-84-5 HCAPLUS
CN 4-Piperidinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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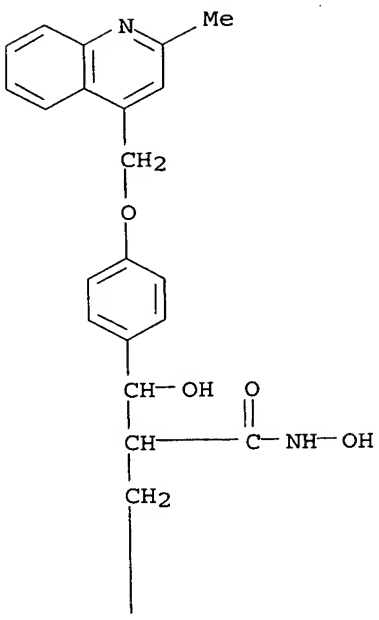

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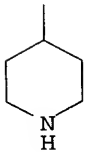

RN 656802-85-6 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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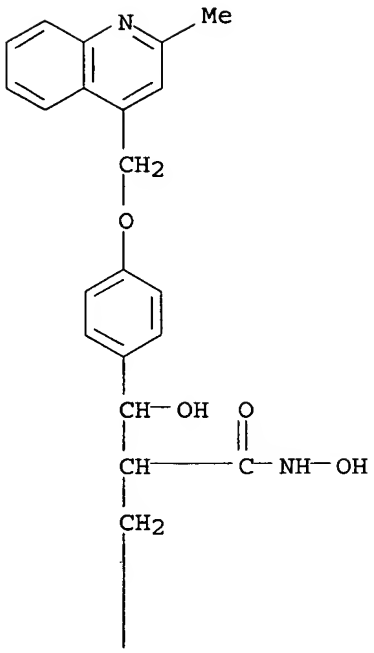

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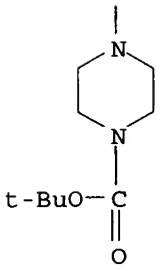

RN 656802-86-7 HCAPLUS
CN 1-Piperazinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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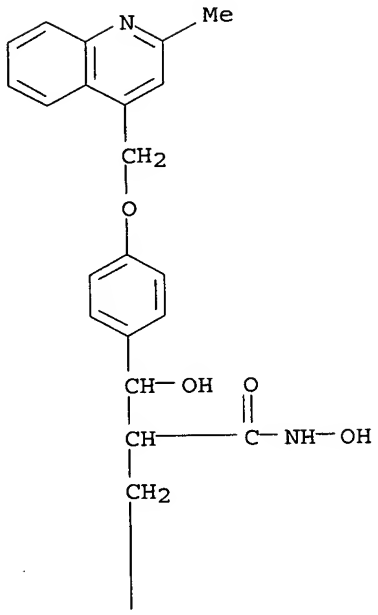

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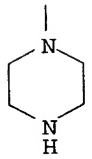
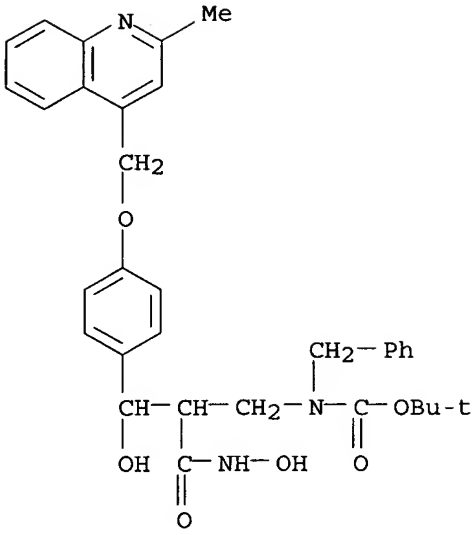
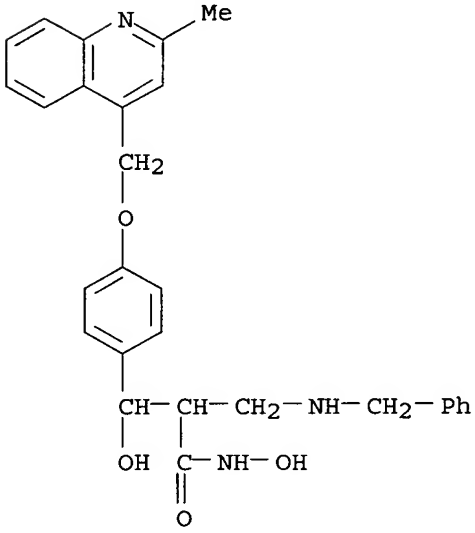


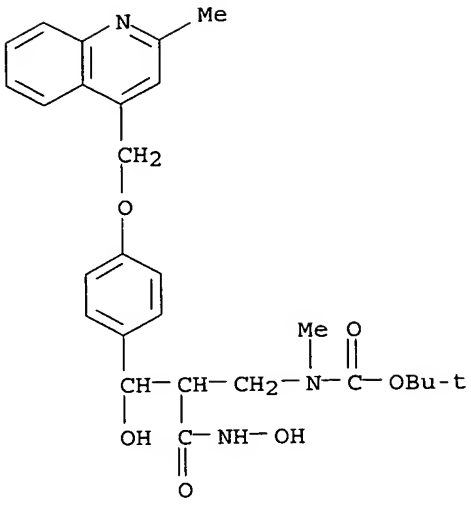
RN 656802-87-8 HCAPLUS
CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl](phenylmethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



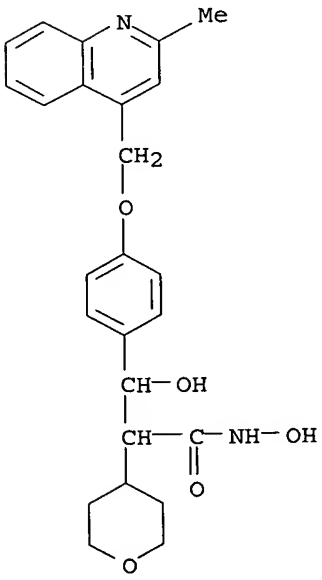
RN 656802-88-9 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-[[(phenylmethyl)amino]methyl]- (9CI) (CA INDEX NAME)



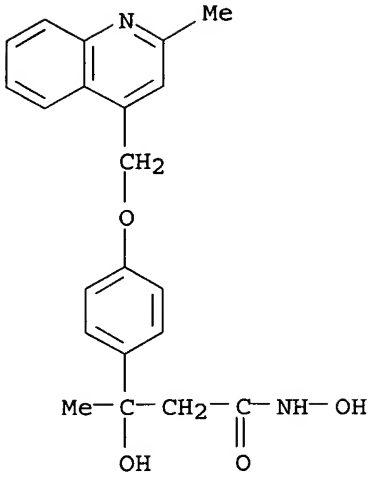
RN 656802-89-0 HCAPLUS
CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



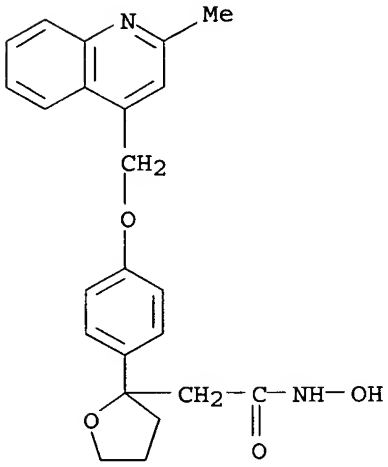
RN 656802-90-3 HCAPLUS
CN 2H-Pyran-4-acetamide, tetrahydro-N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 656802-91-4 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-β-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

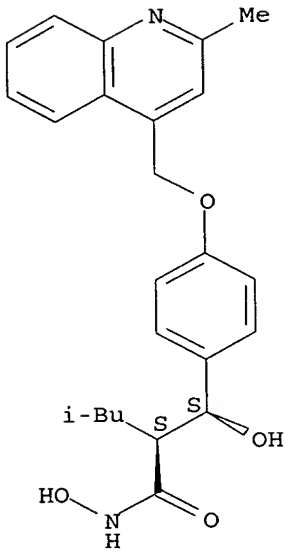


RN 656802-92-5 HCAPLUS
CN 2-Furanacetamide, tetrahydro-N-hydroxy-2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



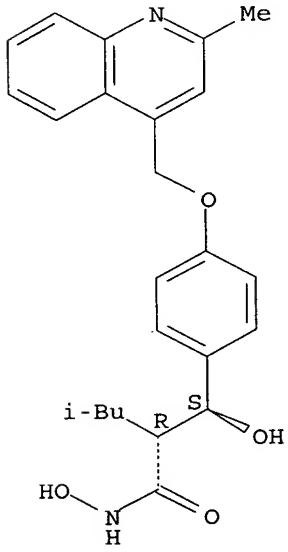
RN 656803-05-3 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



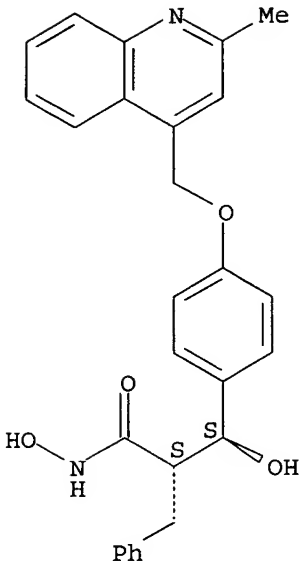
RN 656803-06-4 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



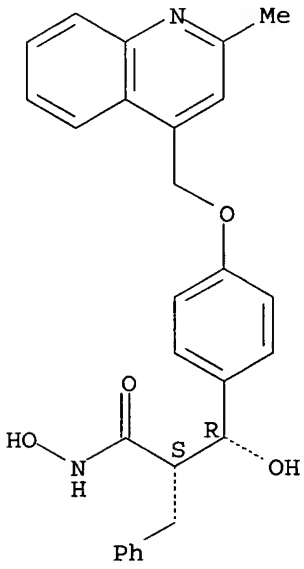
RN 656803-07-5 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



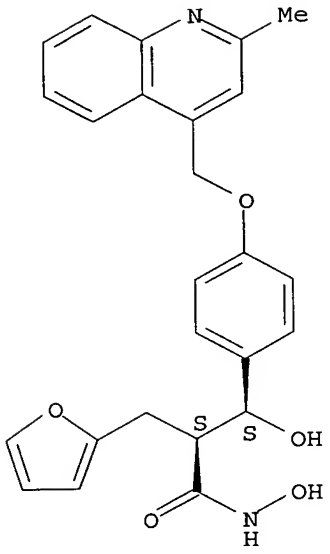
RN 656803-08-6 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



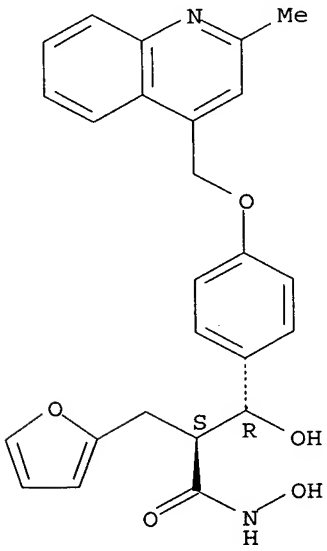
RN 656803-09-7 HCAPLUS
CN 2-Furanpropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



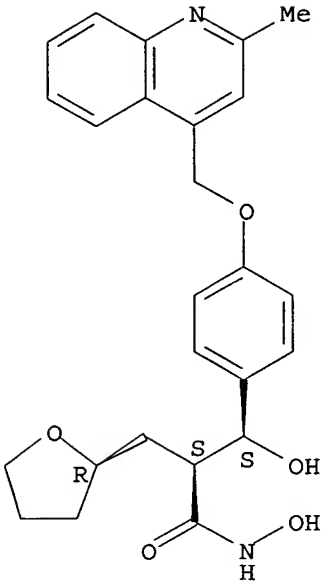
RN 656803-11-1 HCAPLUS
CN 2-Furanpropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



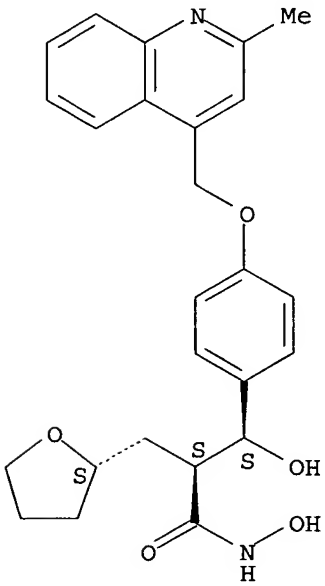
RN 656803-12-2 HCAPLUS
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



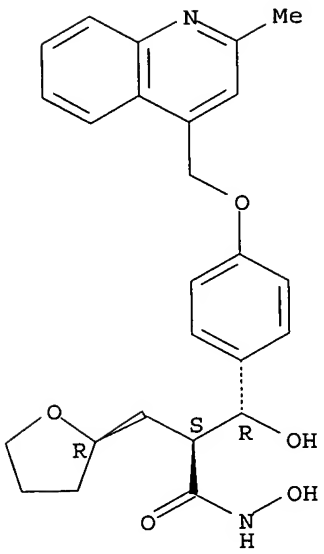
RN 656803-14-4 HCAPLUS
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



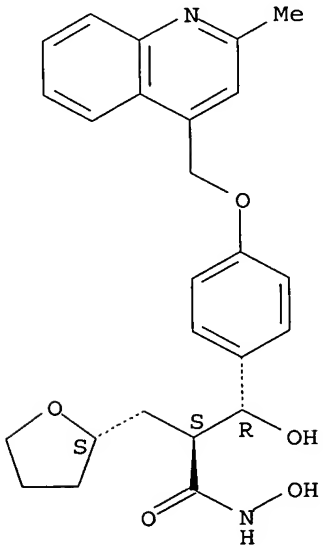
RN 656803-16-6 HCAPLUS
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



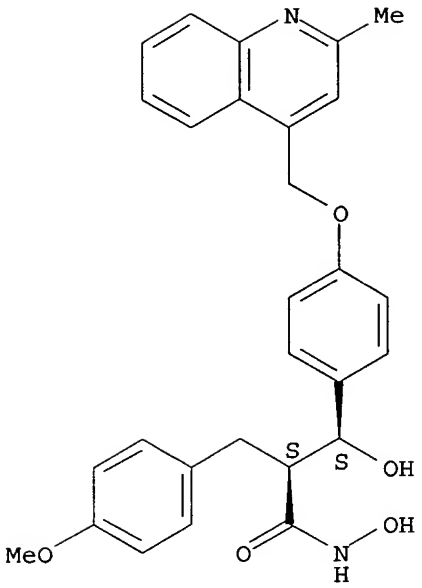
RN 656803-18-8 HCAPLUS
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



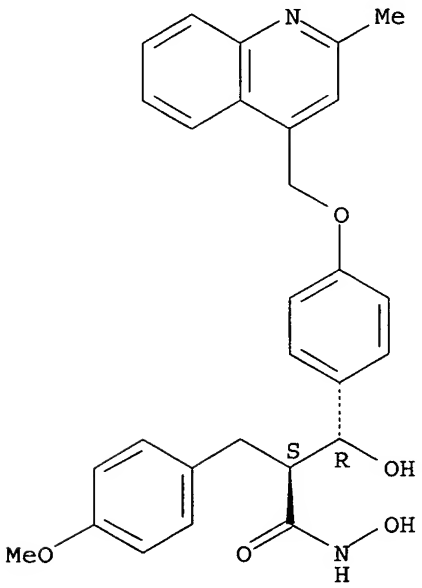
RN 656803-20-2 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



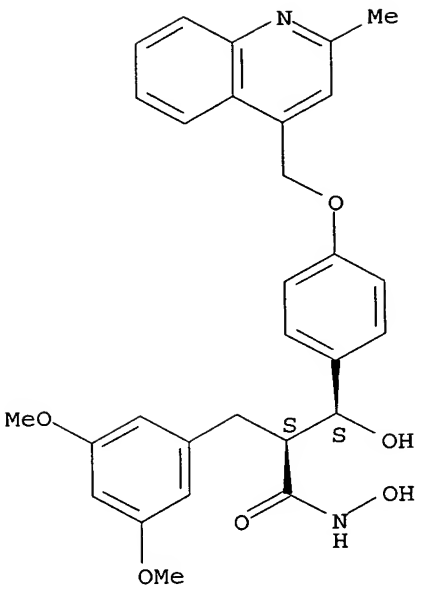
RN 656803-22-4 HCAPLUS
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



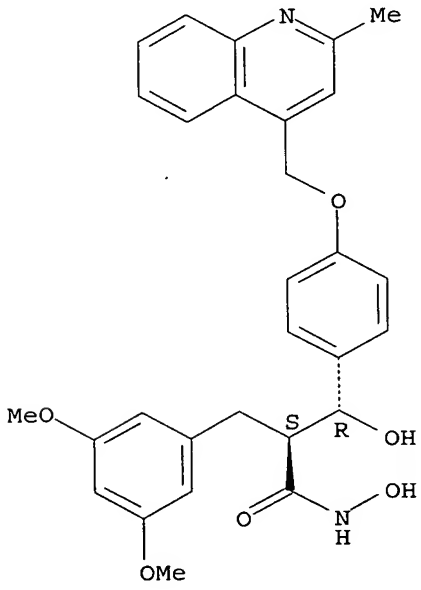
RN 656803-24-6 HCAPLUS
CN Benzenepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



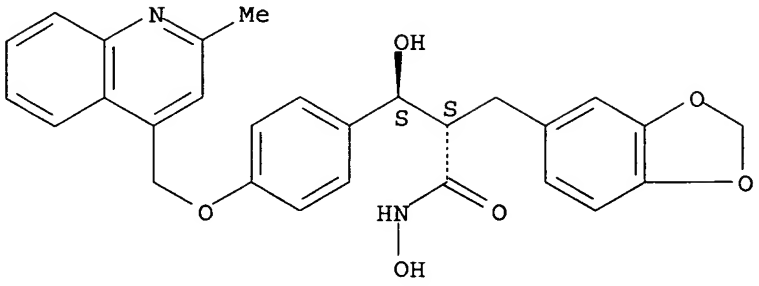
RN 656803-26-8 HCAPLUS
CN Benzenepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



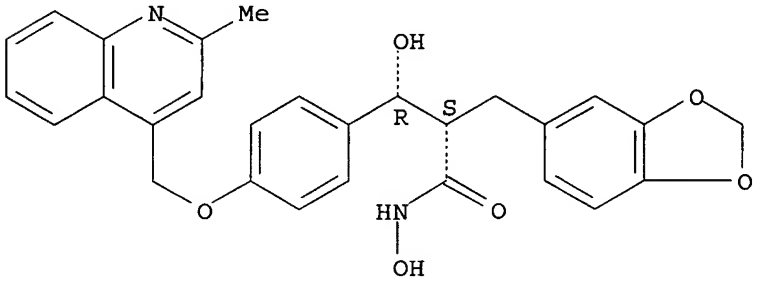
RN 656803-28-0 HCAPLUS
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



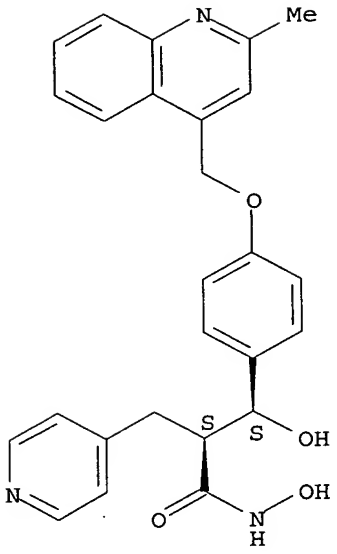
RN 656803-30-4 HCAPLUS
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



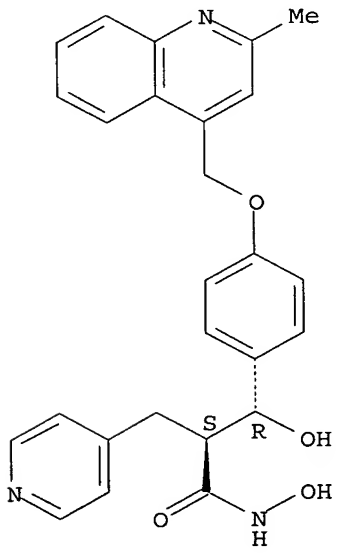
RN 656803-32-6 HCAPLUS
CN 4-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



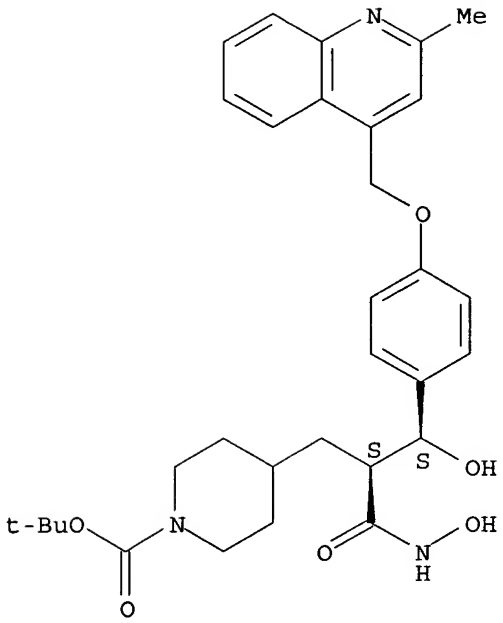
RN 656803-33-7 HCAPLUS
CN 4-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



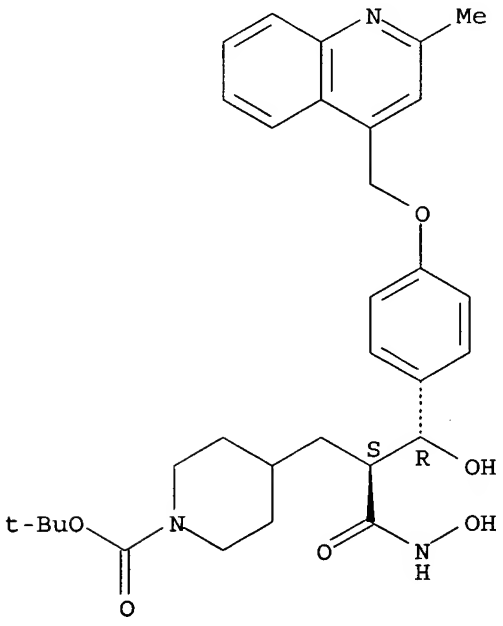
RN 656803-35-9 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656803-36-0 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(S)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L66 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1995:931621 HCAPLUS
DOCUMENT NUMBER: 124:146141
TITLE: N-Hydroxy-N-[4-(2-phenyloxazolyl- and

-thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low density lipoprotein

INVENTOR(S): Malamas, Michael S.; Nelson, James A.
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5459154	A	19951017	US 1993-148603	19931108
US 5504097	A	19960402	US 1995-423061	19950417
PRIORITY APPLN. INFO.:			US 1993-148603	A3 19931108

OTHER SOURCE(S): MARPAT 124:146141
ED Entered STN: 21 Nov 1995
AB This invention relates to compds. having 5-lipoxygenase inhibiting properties and inhibition of oxidative modification of low d. lipoprotein which have the formula I wherein: R1 and R3 are independently hydrogen, halogen, C1-C6 alkyl, C1-C6 alkoxy, trifluoromethyl, or C1-C6 trifluoroalkoxy; R2 is hydrogen or methyl; R4 is hydrogen, Me or hydroxy; R5 is hydrogen, NH2, C1-C6 alkyl, C6-C10 aryl, C6-C10 aryl-C1-C6 alkylene, or N:CMe2; X and Y are independently O or S; and n is 0 or 1; or a pharmaceutically acceptable salt thereof. Compds. which inhibit 5-lipoxygenase are useful in the treatment of diseases mediated by leukotrienes such as inflammation or bronchoconstriction. Compds. which inhibit oxidative metabolism of low d. lipoprotein are useful in the inhibition of atherosclerotic plaque formation. Thus, e.g., carbamoylation of N-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)benzyl]hydroxylamine (preparation given) with trimethylsilyl isocyanate afforded 1-hydroxy-1-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy)benzyl]urea (I; R1 = R3 = R4 = R5 = H, R2 = Me, n = 0, Y = O) which exhibited 69% inhibition of LTB4 synthesis at 25 mg/kg p.o. in the reverse passive Arthus pleurisy assay in rats, 38% inhibition of bronchoconstriction (at 10 mg/kg i.v.) in guinea pigs induced by exogenous antigen, and inhibition of copper ion mediated oxidation of low d. lipoprotein with IC50 = 1.1 μM.
IC ICM C07D263-32
ICS C07D277-30; A61K031-425; A61K031-42
INCL 514374000
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST hydroxyurea phenyloxazolylmethoxybenzyl phenylthiazolylmethoxybenzyl lipoxygenase inhibitor; oxazolylmethoxybenzylhydroxyurea lipoxygenase inhibitor; thiazolylmethoxybenzylhydroxyurea lipoxygenase inhibitor; low density lipoprotein antioxidant oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; bronchodilator oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; antiinflammatory oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea; antiatherosclerotic oxazolylmethoxybenzylhydroxyurea thiazolylmethoxybenzylhydroxyurea
IT Antioxidants
Bronchodilators
Inflammation inhibitors
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT Antiarteriosclerotics
(antiatherosclerotics, N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 173191-85-0P 173191-87-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 173173-26-7P 173173-27-8P 173173-28-9P 173173-29-0P 173173-30-3P
173173-31-4P 173173-32-5P 173173-33-6P 173173-34-7P 173173-35-8P
173173-36-9P 173173-37-0P 173173-38-1P 173191-80-5P 173191-81-6P
173191-82-7P 173191-83-8P **173191-84-9P** 173191-86-1P
173191-88-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 80619-02-9, 5-Lipoxygenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT 67-64-1, Acetone, reactions 99-93-4, 4'-Hydroxyacetophenone 110-87-2, Dihydropyran 123-08-0, 4-Hydroxybenzaldehyde 1195-45-5, 4-Fluorophenylisocyanate 1198-84-1, DL-4-Hydroxymandelic acid 2525-62-4, N-Hexyl isocyanate 30494-97-4, 4-(Chloromethyl)-2-phenyloxazole 103788-61-0, 4-Chloromethyl-5-methyl-2-phenyloxazole 141580-65-6, N,O-Bis(carbo-phenoxy)hydroxylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

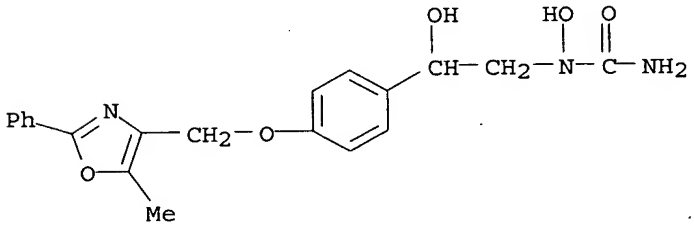
IT 103789-66-8P 103789-67-9P 103789-68-0P 173191-89-4P 173191-90-7P
173191-91-8P 173191-92-9P 173191-93-0P 173191-94-1P 173191-95-2P
173191-96-3P 173191-97-4P 173191-98-5P 173191-99-6P 173192-00-2P
173192-01-3P 173192-02-4P 173192-03-5P 173192-04-6P 173192-05-7P
173192-06-8P 173192-07-9P 173192-08-0P 173192-09-1P 173192-10-4P
173192-11-5P 173192-12-6P **173192-13-7P** 173192-14-8P
173192-15-9P 173192-16-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

IT **173191-84-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas

as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173191-84-9 HCAPLUS

CN Urea, N-hydroxy-N-[2-hydroxy-2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]ethyl]- (9CI) (CA INDEX NAME)



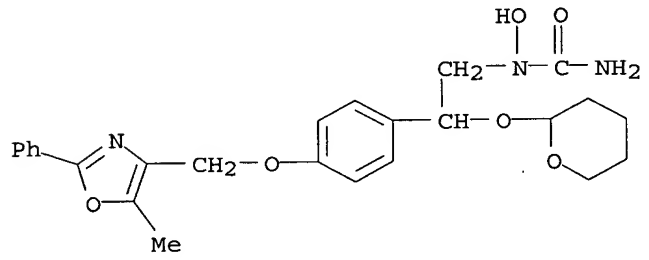
IT **173192-13-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173192-13-7 HCAPLUS

CN Urea, N-hydroxy-N-[2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]-2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)



L66 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 1995:227606 HCAPLUS

DOCUMENT NUMBER: 123:55714

TITLE: Aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis

INVENTOR(S): Brooks, Dee W.; Kolasa, Teodozy J.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: U.S., 15 pp. Cont.-in-part of U.S. Ser. No. 969,898, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5358955	A	19941025	US 1993-71737	19930602
CA 2136076	AA	19940511	CA 1993-2136076	19931012

WO 9410148 A1 19940511 WO 1993-US9752 19931012
W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
EP 666849 A1 19950816 EP 1993-923854 19931012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE
JP 08502749 T2 19960326 JP 1993-511096 19931012
PRIORITY APPLN. INFO.: US 1992-969898 B2 19921030
US 1993-71737 A 19930602
WO 1993-US9752 W 19931012
OTHER SOURCE(S): MARPAT 123:55714
ED Entered STN: 06 Dec 1994
AB The present invention relates to a compound of the formula I or a pharmaceutically acceptable salt thereof (wherein W is selected from optionally substituted pyridyl, naphthyl, and quinolyl; dotted line represents optional valence bond; e.g., for single bond, Z = e.g., CO2NR2R3, and for double bond, Z = e.g., :NOCHR4CO2NR2R3; A = C1-6-alkylene; R1 = e.g., C3-8-cycloalkyl) which inhibits lipoxygenase enzyme activity and leukotriene biosynthesis and is useful in the treatment of inflammatory disease states; also disclosed are leukotriene biosynthesis inhibiting compns. and a method for inhibiting lipoxygenase enzyme activity and leukotriene biosynthesis. In vitro inhibitory potencies against stimulated LTB4 polymorphonuclear leukocytes: IC50 (μmol) in the range 0.033-1.65. Inhibition of the biosynthesis of leukotrienes in vivo after oral administration of compound was determined using a rat peritoneal anaphylaxis model: compds. of this invention prevent the formation of leukotrienes in this model in a range of 1-200 μmol/kg. Pharmaceutical compns. were given.
IC ICM C07D215-14
ICS C07D213-30; A61K031-47; A61K031-44
INCL 514311000
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 25, 63
ST leukotriene biosynthesis inhibitor heteroarylmethoxyphenyl arylmethoxyphenyl; lipoxygenase enzyme inhibitor heteroarylmethoxyphenyl arylmethoxypheny
IT Leukotrienes
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(biosynthesis inhibition; aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)
IT 158606-72-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)
IT 158606-73-6P 158606-74-7P 158606-77-0P 158606-79-2P 158606-84-9P 158606-85-0P 158606-88-3P 164578-83-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)
IT 100-83-4, 3-Hydroxybenzaldehyde 108-85-0, Cyclohexyl bromide 123-08-0 137-43-9, Bromocyclopentane 524-38-9, N-Hydroxyphthalimide 623-51-8, Ethyl thioglycolate 939-26-4, 2-(Bromomethyl)naphthalene 2404-35-5, Cycloheptyl bromide 3747-74-8, 2-Chloromethylquinoline hydrochloride 6959-47-3, 2-Chloromethylpyridine hydrochloride 13633-25-5, 1-Bromo-4-phenylbutane 14199-15-6, Methyl 4-hydroxyphenylacetate 64473-35-4 164578-88-5

RL: RCT (Reactant); RACT (Reactant or reagent)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

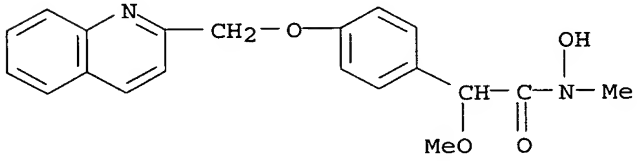
IT 76529-98-1P, 2-Methoxy-2-(4-hydroxyphenyl)acetic acid methyl ester 103119-21-7P 120159-59-3P, 4-(2-Quinolinyl-methoxy)benzaldehyde 123723-93-3P, Methyl 4-(quinolin-2-yl-methoxy)phenylacetate 127481-38-3P 128253-06-5P 128253-07-6P 128253-08-7P 128253-09-8P 128253-11-2P 128253-12-3P 128253-13-4P 128253-14-5P 143055-94-1P 158606-69-0P 158606-70-3P 158606-71-4P, 4-(2-Pyridylmethoxy)phenylacetic acid methyl ester 158606-89-4P 158606-90-7P 158606-91-8P 158606-95-2P 158606-96-3P 158606-97-4P 158606-98-5P 158606-99-6P 158607-00-2P 158607-01-3P 158607-02-4P 158607-03-5P 158607-04-6P 164578-81-8P 164578-84-1P 164578-85-2P 164578-86-3P 164578-87-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT 2550-36-9P, (Bromomethyl)cyclohexane 158606-75-8P 158606-78-1P 158606-80-5P **158606-81-6P** 158606-82-7P **158606-83-8P** 158606-87-2P 164578-82-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

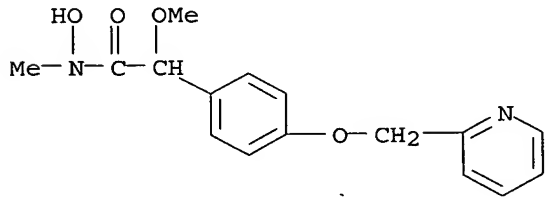
IT 9029-60-1, Lipoxygenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

IT **158606-81-6P 158606-83-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(aryl and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis)

RN 158606-81-6 HCAPLUS
CN Benzeneacetamide, N-hydroxy-α-methoxy-N-methyl-4-(2-quinolinylmethoxy)- (9CI) (CA INDEX NAME)



RN 158606-83-8 HCAPLUS
CN Benzeneacetamide, N-hydroxy-α-methoxy-N-methyl-4-(2-pyridinylmethoxy)- (9CI) (CA INDEX NAME)



L66 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1995:277045 HCAPLUS
DOCUMENT NUMBER: 122:46487
TITLE: CAT-1 inhibitors, their synthesis, pharmaceutical compositions, and methods of use
INVENTOR(S): Guthrie, Robert W.; Mullin, John G., Jr.; Kachensky, David F.; Kierstead, Richard W.; Tilley, Jefferson W.; Heathers, Guy P.; Higgins, Alan J.; Lemahieu, Ronald A.
PATENT ASSIGNEE(S): Hoffman-La Roche Inc., USA
SOURCE: U.S., 85 pp. Cont.-in-part of U.S. Ser. No. 698, 014, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5344843	A	19940906	US 1992-850620	19920313
RU 2059603	C1	19960510	RU 1992-5011784	19920131
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
AT 136018	E	19960415	AT 1992-107135	19920427
AU 9216003	A1	19921112	AU 1992-16003	19920504
AU 653398	B2	19940929		
CA 2068076	AA	19921110	CA 1992-2068076	19920506
ZA 9203279	A	19930127	ZA 1992-3279	19920506
NO 9201840	A	19921110	NO 1992-1840	19920508
HU 63602	A2	19930928	HU 1992-1538	19920508
JP 05279353	A2	19931026	JP 1992-143375	19920508
JP 07107060	B4	19951115		
RO 109938	B1	19950728	RO 1992-622	19920508
BR 9201769	A	19921229	BR 1992-1769	19920511
PRIORITY APPLN. INFO.:			US 1991-698014 B2	19910509
			US 1992-850620 A	19920313

OTHER SOURCE(S): MARPAT 122:46487
ED Entered STN: 07 Jan 1995
AB The invention relates to compds. I (R1 = OH; R2, R3 = H, alkyl, aryl, alkoxy, etc.; X, Y together = O, or one is amino and other is H; Z = S, CR2=CR2'; A = bond, O, S, SO, CHCH, etc.; B = bond, O, S, SO, etc.; Q = Ph, cyclohexyl, pyridinyl, etc.; n = 1-6) and their pharmaceutically acceptable salts, and when appropriate, enantiomers, racemates, diastereomers or mixts. thereof or geometric isomer or mixts. thereof, and pharmaceutically acceptable salts thereof. The compds. inhibit carnitine acyltransferase 1 (CAT-1) and are therefore useful in the prevention of injury to ischemic tissue, and can limit infarct size, improve cardiac function and prevent arrhythmias during and following a myocardial infarction. 5-[[2-(2-Naphthalenyloxy)ethyl]oxy]-α-oxo-2-thiopheneacetic acid (preparation given) inhibited CAT-1 with an IC50 = 0.05 μM. Tablet and capsule formulations containing 4-[2-(2-naphthyloxy)ethoxy]-α-oxobenzeneacetic acid are presented.
IC ICM A61K031-19
ICS A61K031-38; C07C065-40; C07D333-32
INCL 514473000
CC 1-8 (Pharmacology)
Section cross-reference(s): 7, 25, 27, 63

ST carnitine acyltransferase inhibitor compd; ischemia carnitine acyltransferase inhibitor

IT Ischemia
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds. for prevention of injury from)

IT Pharmaceutical dosage forms
(capsules, synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT Heart, disease
(infarction, synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds. for prevention of injury from)

IT Pharmaceutical dosage forms
(tablets, synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 39386-49-7, Carnitine acyltransferase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor compds.; synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 145794-10-1P 145795-19-3P 145795-25-1P 145795-27-3P 145795-76-2P
145795-81-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 145794-12-3P 145794-14-5P 145794-16-7P 145794-21-4P 145794-23-6P
145794-25-8P 145794-27-0P 145794-29-2P 145794-31-6P 145794-33-8P
145794-35-0P 145794-37-2P 145794-39-4P 145794-41-8P 145794-43-0P
145794-45-2P 145794-47-4P 145794-49-6P 145794-51-0P 145794-53-2P
145794-55-4P 145794-57-6P 145794-59-8P 145794-61-2P 145794-63-4P
145794-65-6P 145794-67-8P 145794-69-0P 145794-71-4P 145794-73-6P
145794-75-8P 145794-77-0P 145794-79-2P 145794-82-7P 145794-86-1P
145794-90-7P 145794-92-9P 145794-94-1P 145794-98-5P 145794-99-6P
145795-01-3P 145795-02-4P 145795-04-6P 145795-05-7P 145795-06-8P
145795-07-9P 145795-08-0P 145795-09-1P 145795-10-4P 145795-11-5P
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145795-18-2P 145795-20-6P 145795-21-7P 145795-23-9P 145795-24-0P
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145795-38-6P 145795-39-7P 145795-41-1P 145795-43-3P 145795-44-4P
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145795-50-2P 145795-51-3P 145795-52-4P 145795-53-5P 145795-55-7P
145795-56-8P 145795-57-9P 145795-58-0P 145795-59-1P 145795-60-4P
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145795-73-9P 145795-74-0P 145795-75-1P 145795-77-3P 145795-79-5P
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145795-87-5P 145795-88-6P 145795-89-7P 145795-90-0P 145795-91-1P
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145797-00-8P 146548-36-9P 146548-37-0P 146548-40-5P 146548-41-6P
146548-42-7P 146548-43-8P 146548-44-9P 146572-66-9P 160062-09-9P
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160062-21-5P 160062-22-6P 160062-23-7P 160062-24-8P
160062-25-9P 160062-26-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 145794-09-8 145795-95-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 56-81-5, 1,2,3-Propanetriol, reactions 57-14-7, 1,1-Dimethylhydrazine 79-37-8, Oxalyl chloride 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 92-44-4, 2,3-Dihydroxynaphthalene 93-20-9 100-39-0, Benzyl bromide 108-00-9, N,N-Dimethylethylenediamine 108-01-0 111-42-2, Diethanolamine, reactions 112-27-6 124-40-3, Dimethylamine, reactions 141-43-5, reactions 403-14-5, 3-Fluoro-4-hydroxyacetophenone 460-00-4, 4-Fluorobromobenzene 588-63-6, (3-Bromopropoxy)benzene 589-10-6, β-Bromophenetole 593-56-6, Methoxylamine hydrochloride 613-54-7, Bromomethyl 2-naphthyl ketone 637-59-2, 3-Bromo-1-phenylpropane 769-39-1, 2,3,5,6-Tetrafluorophenol 875-59-2, 4-Hydroxy-2-methylacetophenone 876-02-8, 4-Hydroxy-3-methylacetophenone 937-14-4, 3-Chloroperbenzoic acid 939-26-4, 2-Bromomethylnaphthalene 1137-41-3, p-Aminobenzophenone 1200-03-9, (4-Bromobutoxy)benzene 1940-28-9, 4-Bromo-3,5-dichlorophenol 2243-83-6, 2-Naphthoyl chloride 2450-71-7, Propargylamine 2478-38-8, 3,5-Dimethoxy-4-hydroxyacetophenone 2605-67-6, (Carbomethoxymethylene)triphenylphosphorane 2687-12-9, (3-Chloro-1-propenyl)benzene 2687-43-6 2892-29-7, 3-Chloro-4-hydroxyacetophenone 2967-54-6, 3,5-Difluoro-4-hydroxybenzonitrile 3245-62-3 3332-29-4 3747-74-8, 2-Chloromethylquinoline hydrochloride 3814-20-8 4229-44-1, N-Methylhydroxylamine hydrochloride 4442-79-9, Cyclohexaneethanol 4755-77-5, Ethyl oxalyl chloride 5264-15-3, 4-Pyridinebutanol 5452-37-9, Cyclooctylamine 5470-11-1, Hydroxylamine hydrochloride 5856-77-9, 2,2-Dimethylbutyryl chloride 6089-04-9 6315-52-2 6322-56-1, 4-Hydroxy-3-nitroacetophenone 6707-01-3, Chloromethoxybenzene 7664-41-7, Ammonia, reactions 13246-14-5 16427-44-4 16839-97-7 17044-70-1, 3,5-Dichloro-4-hydroxyacetophenone 20009-28-3 20020-27-3 21087-29-6 21886-62-4 22118-09-8, Bromoacetyl chloride 22921-72-8 23287-26-5 23314-24-1 24484-55-7 27064-92-2 31076-84-3 32462-30-9, (S)-4-Hydroxyphenylglycine 34604-52-9 36754-60-6, 2-Chloromethylbenzofuran 37595-74-7 38078-09-0, Diethylaminosulfur trifluoride 38250-16-7 38945-21-0 39199-93-4 39500-31-7 40299-87-4, 4-(Bromoacetyl)morpholine 40786-20-7 40926-77-0 41656-75-1 51795-97-2 53542-78-2 54537-30-3 60753-14-2, 3-Pyridinebutanol 61236-14-4 62001-72-3 63649-88-7 63649-90-1 63650-21-5 64957-86-4 65512-08-5 66340-55-4 68301-59-7 69189-03-3 70080-54-5 76469-33-5 77923-27-4, 2-(Cyclooctyloxy)ethanol 86902-13-8 87271-22-5 87723-22-6, 2-(4-Bromobutoxy)naphthalene 91540-82-8 93957-49-4 98619-07-9 98793-02-3 99690-59-2 107890-32-4 109083-77-4 113272-40-5 120895-36-5 123843-57-2, 2,6-Difluoro-4-hydroxybenzonitrile 128988-59-0 130954-91-5 132464-59-6 141482-06-6 145794-07-6 145794-08-7 145794-87-2 145794-88-3 145795-03-5 145796-98-1 145797-06-4 145797-56-4 145798-06-7 145798-30-7 145798-31-8 145798-32-9 145798-34-1 145798-35-2 145798-36-3 145798-37-4 145798-38-5 145798-39-6 145798-40-9 145798-42-1 145798-43-2 145798-44-3 145798-45-4 145798-46-5 145798-47-6 145798-49-8 145798-50-1 145798-51-2 145798-52-3 145798-53-4 145798-54-5 145798-55-6 145798-56-7 145798-57-8 145798-58-9 145798-59-0 145798-60-3 145798-61-4 145798-62-5 145798-63-6 145798-64-7 145798-65-8 160062-29-3 160062-43-1 160062-44-2D, γ-oxo-2-naphthalenebutanoic acid 160062-46-4 160062-47-5

RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT 69651-48-5P 89012-04-4P 101125-34-2P 131003-09-3P 134748-95-1P
145794-11-2P 145794-13-4P 145794-15-6P 145794-17-8P 145794-19-0P
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145794-32-7P 145794-34-9P 145794-36-1P 145794-38-3P 145794-40-7P
145794-42-9P 145794-44-1P 145794-46-3P 145794-48-5P 145794-50-9P
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145794-72-5P 145794-74-7P 145794-76-9P 145794-78-1P 145794-81-6P
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145798-04-5P 145798-05-6P 145798-07-8P 145798-08-9P 145798-09-0P
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145798-20-5P 145798-21-6P 145798-22-7P 145798-23-8P 145798-24-9P
145798-26-1P 145798-27-2P 145798-28-3P 146548-38-1P 160062-27-1P
160062-28-2P 160062-31-7P 160062-32-8P 160062-33-9P 160062-34-0P
160062-35-1P 160062-36-2P 160062-37-3P 160062-38-4P 160062-39-5P
160062-40-8P 160062-41-9P 160062-42-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

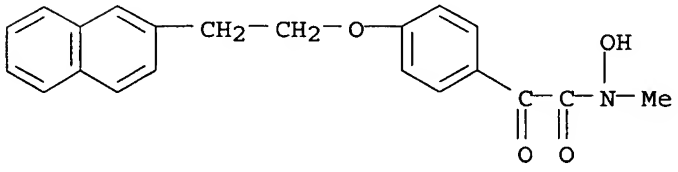
IT 145794-20-3P 145795-17-1P 145795-22-8P 145795-35-3P 145795-36-4P
145795-37-5P 145795-40-0P 145795-54-6P 145795-67-1P 145796-09-4P
145796-80-1P 145796-85-6P 145798-25-0P 146548-39-2P 160062-30-6P

RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

IT **160062-21-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and pharmaceutical compns. and use of carnitine

acyltransferase inhibitor compds.)
RN 160062-21-5 HCAPLUS
CN Benzeneacetamide, N-hydroxy-N-methyl-4-[2-(2-naphthalenyl)ethoxy]-α-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:964135 HCAPLUS
DOCUMENT NUMBER: 138:24543
TITLE: Preparation of benzyloxyphenyloxobutyrates and related compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini; Von Borstel, Reid W.; Hodge, Kirvin L.
PATENT ASSIGNEE(S): Wellstat Therapeutics Corporation, USA; Bamat, Michael K.
SOURCE: PCT Int. Appl., 242 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002100341	A2	20021219	WO 2002-US18388	20020612
WO 2002100341	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2450221	AA	20021219	CA 2002-2450221	20020612
US 2003149107	A1	20030807	US 2002-167839	20020612
EP 1461323	A2	20040929	EP 2002-744271	20020612
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2005501012	T2	20050113	JP 2003-503168	20020612
US 2004077896	A1	20040422	US 2003-684644	20031014
US 6924314	B2	20050802		
US 2004092518	A1	20040513	US 2003-684735	20031014
US 2004092516	A1	20040513	US 2003-685183	20031014
US 6946491	B2	20050920		
US 2004097585	A1	20040520	US 2003-684730	20031014
US 6916848	B2	20050712		
US 2004236100	A1	20041125	US 2003-684660	20031014
US 6858602	B2	20050222		

US 2004267025	A1	20041230	US 2003-684740	20031014
US 2004242692	A1	20041202	US 2004-865088	20040610
US 2005004115	A1	20050106	US 2004-892950	20040716
US 2005090555	A1	20050428	US 2004-5449	20041206
			US 2001-297282P	P 20010612
			US 2002-167839	A3 20020612
			WO 2002-US18388	W 20020612
			US 2003-685183	A3 20031014
			US 2004-865088	A1 20040610

PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 138:24543

ED Entered STN: 20 Dec 2002

AB Biol. active title compds. [I; n = 1, 2; m, q, p = 0, 1; R5 = alkyl; R9 = H, halo, alkoxy; A = (halo-, alkyl-, perfluoromethyl-, alkoxy-, perfluoromethoxy-substituted) Ph, (Me-, Et-substituted) cycloalkyl, 5-6 membered heteroarom. ring having 1-2 N, S, O atoms; X = CH2, Q = OR1, R1 = Et; or X = CH2CR12R13, CH2CH(NHAc), Q = OR1, R1 = H, alkyl; or X = CH2CH2, Q = NR10R11; R12, R13 = H, Me; 1 of R10, R11 = H, alkyl, OH, the other = H, alkyl], were prepared Thus, 4-(2-fluorobenzyloxy)acetophenone (preparation given) in THF and DMPU was treated with a solution of Li bis(trimethylsilyl)amide at -60°; after 10 min, tert-Bu bromoacetate was added followed by stirring for an addnl. 10 min and warming to room temperature for 4 h to give tert-Bu 4-[4-(2-fluorobenzyloxy)phenyl]-4-oxobutyrate. The latter was stirred with CF3CO2H in CH2Cl2 to give 4-[4-(2-fluorobenzyloxy)phenyl]-4-oxobutyric acid. Tested I showed antidiabetic activity in a variety of tests. I are useful in treatment of various metabolic disorders such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis.

IC ICM A61K

CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 27, 28

ST benzyloxyphenyloxobutyrate prepn metabolic disorder treatment; diabetes treatment benzyloxyphenyloxobutyrate prepn; insulin resistance diabetes mellitus fatty liver hyperlipidemia treatment benzyloxyphenyloxobutyrate; cachexia obesity atherosclerosis hypertension arteriosclerosis treatment benzyloxyphenyloxobutyrate prepn; nephropathy neuropathy retinopathy foot ulceration cataract treatment benzyloxyphenyloxobutyrate prepn

IT Liver, disease
(fatty, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Foot
(foot ulceration treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Autoimmune disease
(insulin-dependent diabetes mellitus, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Diabetes mellitus
(insulin-dependent, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Nerve, disease
(neuropathy, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Antiarteriosclerotics
Antidiabetic agents
Antihypertensives

Antiobesity agents
Human
Hypolipemic agents
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Eye, disease
(retinopathy, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT Arteriosclerosis
Atherosclerosis
Cachexia
Cataract
Diabetes mellitus
Hypertension
Kidney, disease
Obesity
(treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 478162-80-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 6686-25-5P 478162-45-7P 478162-46-8P 478162-47-9P 478162-48-0P
478162-49-1P 478162-50-4P 478162-51-5P 478162-52-6P 478162-53-7P
478162-54-8P 478162-55-9P 478162-56-0P 478162-57-1P 478162-58-2P
478162-59-3P 478162-60-6P 478162-61-7P 478162-62-8P 478162-63-9P
478162-64-0P 478162-65-1P 478162-66-2P 478162-67-3P 478162-68-4P
478162-69-5P 478162-70-8P 478162-71-9P 478162-72-0P 478162-73-1P
478162-74-2P 478162-75-3P 478162-76-4P 478162-77-5P 478162-78-6P
478162-79-7P 478162-81-1P 478162-82-2P 478162-83-3P 478162-84-4P
478162-85-5P 478162-86-6P 478162-87-7P 478162-88-8P 478162-89-9P
478162-90-2P 478162-91-3P **478162-92-4P** 478162-93-5P
478162-94-6P 478162-95-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 89-92-9, 2-Methylbenzyl bromide 99-93-4, 4-Hydroxyacetophenone
100-44-7, Benzyl chloride, reactions 105-36-2, Ethyl bromoacetate
109-83-1, 2-Methylaminoethanol 118-93-4 121-71-1 395-44-8,
2-Trifluoromethylbenzyl bromide 402-49-3, 4-Trifluoromethylbenzyl bromide 446-48-0, 2-Fluorobenzyl bromide 446-51-5, 2-Fluorobenzyl alcohol 456-41-7, 3-Fluorobenzyl bromide 459-46-1, 4-Fluorobenzyl bromide 600-00-0, Ethyl 2-bromoisobutyrate 611-17-6, 2-Chlorobenzyl bromide 612-16-8, 2-Methoxybenzyl alcohol 623-05-2, 4-Hydroxybenzyl alcohol 632-46-2, 2,6-Dimethylbenzoic acid 824-45-3,
2,5-Dimethylbenzyl chloride 1068-90-2, Diethyl acetamidomalonate
2033-24-1, Meldrum's acid 3179-31-5, 1,2,4-Triazole-3-thiol 5292-43-3,
tert-Butyl bromoacetate 5402-55-1, 2-(2-Thienyl)ethanol 5466-06-8,
Ethyl 3-mercaptopropionate 6959-47-3, 2-Picolyl chloride hydrochloride
7051-34-5, Cyclopropylmethyl bromide 13670-99-0, 2,6-Difluoroacetophenone 14191-95-8, 4-Hydroxybenzyl cyanide 16475-90-4,
Methyl 2-hydroxy-5-acetylbenzoate 17247-58-4, Cyclobutylmethyl bromide
23915-07-3, 2,4-Difluorobenzyl bromide 50919-06-7 85117-99-3,
2,5-Difluorobenzyl bromide 85118-00-9, 2,6-Difluorobenzyl bromide
90259-27-1, 2-Fluoro-6-methylbenzoic acid 478163-47-2
RL: RCT (Reactant); RACT (Reactant or reagent)

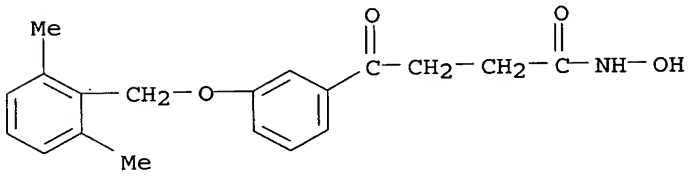
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 17138-28-2P 39971-36-3P, Methyl 2-methoxy-5-acetylbenzoate 50596-33-3P 54696-05-8P, 4-(Benzyloxy)acetophenone 62285-58-9P, 2,6-Dimethylbenzyl Alcohol 68535-61-5P, 2-Methoxy-5-acetylbenzoic acid 72293-94-8P 72293-95-9P 72293-96-0P 74788-82-2P, 2,6-DimethylbenzylAmine 93291-55-5P 93291-62-4P 93748-83-5P 130403-21-3P, N-(2,6-Dimethylbenzyl)phthalimide 170916-37-7P 187532-78-1P 187532-79-2P 187532-84-9P 312592-47-5P 478159-56-7P 478162-96-8P 478162-97-9P 478162-98-0P 478162-99-1P 478163-00-7P 478163-01-8P 478163-02-9P 478163-03-0P 478163-04-1P 478163-05-2P 478163-06-3P 478163-07-4P 478163-08-5P 478163-09-6P 478163-10-9P 478163-11-0P 478163-12-1P 478163-13-2P 478163-14-3P 478163-15-4P 478163-16-5P 478163-17-6P 478163-18-7P 478163-19-8P 478163-20-1P 478163-21-2P 478163-22-3P 478163-23-4P 478163-24-5P 478163-25-6P 478163-26-7P 478163-27-8P 478163-28-9P 478163-29-0P 478163-30-3P 478163-31-4P 478163-32-5P 478163-33-6P 478163-34-7P 478163-35-8P 478163-36-9P 478163-37-0P 478163-38-1P 478163-39-2P 478163-40-5P 478163-41-6P 478163-42-7P 478163-43-8P 478163-44-9P 478163-45-0P 478163-46-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(resistance, treatment; preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

IT **478162-92-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 HCAPLUS
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:655667 HCAPLUS
DOCUMENT NUMBER: 121:255667
TITLE: Aryl- and heteroarylmethoxyphenyl inhibitors of leukotriene biosynthesis
INVENTOR(S): Brooks, Dee W.; Kolasa, Teodozy
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9410148	A1	19940511	WO 1993-US9752	19931012
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5358955	A	19941025	US 1993-71737	19930602
EP 666849	A1	19950816	EP 1993-923854	19931012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08502749	T2	19960326	JP 1993-511096	19931012
PRIORITY APPLN. INFO.:			US 1992-969898 A	19921030
			US 1993-71737 A	19930602
			WO 1993-US9752 W	19931012

OTHER SOURCE(S): MARPAT 121:255667

ED Entered STN: 26 Nov 1994

AB The invention relates to compds. I and pharmaceutically acceptable salts [wherein A = C1-6 alkylene; R1 = (un)substituted cycloalkyl, alkoxy, PhO, pyridyloxy, Ph, pyridyl, thienyl, furyl, benzofuryl, benzothienyl, or thiazolyl; Z = (singly bound) COONR2R3, CON(OH)R2, OCHR4COONR2R3, SCHR4CON(OH)R2, ON:CHCOONR2R3, (doubly bound) :NOCHR4COONR2R3, etc.; R2, R3, R4 = H, alkyl, hydroxyalkyl; Y = H, alkyl, alkoxy, PhO, halo; n = 0-4; W = (un)substituted pyridyl, naphthyl, or quinolyl]. I inhibit lipoxygenase enzyme activity and leukotriene biosynthesis, and are useful in the treatment of inflammatory disease states. For example, Me 4-(2-quinolylmethoxy)phenylacetate (preparation given) underwent α-alkylation using NaH and cyclohexyl bromide, followed by hydrolysis using NaOH in refluxing MeOH, to give 2-cyclohexyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid. This was converted with ClCO2Bu-iso and Et3N to a mixed anhydride, which then reacted with MeNHOSiMe3 (prepared in situ) to give upon workup title compound II. The IC50 of II for inhibition of Ca ionophore-stimulated LTB4 formation in human polymorphonuclear leukocytes in vitro was 0.033 μM.

IC ICM C07D213-30
ICS C07D215-02; A61K031-44; A61K031-47

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST hydroxyamide pyridylmethoxyphenyl prepn lipoxygenase inhibitor; quinolinylmethoxyphenyl hydroxyamide prepn leukotriene biosynthesis inhibitor; naphthylmethoxyphenyl hydroxyamide prepn antiinflammatory antiallergic

IT Allergy inhibitors
Inflammation inhibitors
(aryl- and heteroarylmethoxyphenyl-containing hydroxyamides)

IT Leukotrienes
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(biosynthesis of, inhibitors of, aryl- and heteroarylmethoxyphenyl-containing hydroxyamides as)

IT 13633-25-5, 1-Bromo-4-phenylbutane 158607-05-7, 1-Bromo-4-(4-chlorophenyl)butane
RL: RCT (Reactant); RACT (Reactant or reagent)
(Grignard reaction of, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 4229-44-1, N-Methylhydroxylamine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation of, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 71160-24-2P, LTB4

RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(biosynthesis of, inhibitors of, aryl- and heteroarylmethoxyphenyl-containing hydroxyamides as)

IT 1198-84-1, 4-Hydroxymandelic acid 16645-06-0, N,N-Dimethylhydroxylamine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of, in preparation of (hetero)aryl-containing hydroxyamides as
lipoxygenase inhibitors)

IT 100-83-4, 3-Hydroxybenzaldehyde 123-08-0, 4-Hydroxybenzaldehyde 524-38-9, N-Hydroxyphthalimide 939-26-4, 2-(Bromomethyl)naphthalene 3747-74-8, 2-Chloromethylquinoline hydrochloride 6959-47-3, 2-Chloromethylpyridine hydrochloride 14199-15-6, Methyl 4-hydroxyphenylacetate
RL: RCT (Reactant); RACT (Reactant or reagent)
(etherification of, in preparation of (hetero)aryl-containing hydroxyamides as
lipoxygenase inhibitors)

IT 63551-74-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors of, aryl- and heteroarylmethoxyphenyl-containing hydroxyamides as)

IT 2921-14-4, Carboxymethoxylamine hemihydrochloride 20295-82-3, Aminooxyacetic acid hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(oximation by, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 298-12-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(oximation of, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT 76529-98-1P, 2-Methoxy-2-(4-hydroxyphenyl)acetic acid methyl ester 120159-59-3P, 4-(2-Quinolinylmethoxy)benzaldehyde 123723-93-3P, Methyl 4-(2-quinolinylmethoxy)phenylacetate 127481-38-3P 128253-06-5P 128253-07-6P 128253-08-7P, 2-Cyclohexyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid methyl ester 128253-09-8P, 2-Cycloheptyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid methyl ester 128253-11-2P 128253-12-3P 128253-13-4P, 2-Cyclohexyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid 128253-14-5P, 2-Cycloheptyl-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid 131340-67-5P, 3-(2-Naphthylmethoxy)benzaldehyde 143055-94-1P 158606-69-0P, 2-Methoxy-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid methyl ester 158606-70-3P, 2-Methoxy-2-[4-(2-quinolinylmethoxy)phenyl]acetic acid 158606-71-4P, 4-(2-Pyridylmethoxy)phenylacetic acid methyl ester 158606-89-4P 158606-90-7P 158606-91-8P 158606-92-9P 158606-93-0P 158606-94-1P 158606-95-2P 158606-96-3P 158606-97-4P 158606-98-5P 158606-99-6P 158607-00-2P 158607-01-3P 158607-02-4P 158607-03-5P 158607-04-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate in preparation of lipoxygenase inhibitors)

IT 158606-72-5P 158606-73-6P 158606-74-7P 158606-75-8P 158606-76-9P 158606-77-0P 158606-78-1P 158606-79-2P 158606-80-5P **158606-81-6P** 158606-82-7P **158606-83-8P** 158606-84-9P 158606-85-0P 158606-86-1P 158606-87-2P 158606-88-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as lipoxygenase inhibitor)

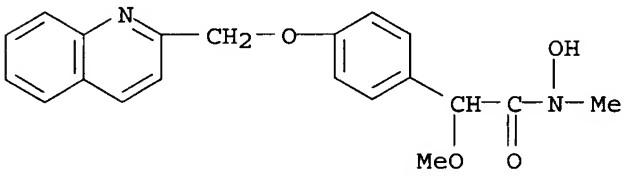
IT 623-51-8, Ethyl thioglycolate

RL: RCT (Reactant); RACT (Reactant or reagent)
(thioetherification of, in preparation of (hetero)aryl-containing hydroxyamides
as lipoxygenase inhibitors)

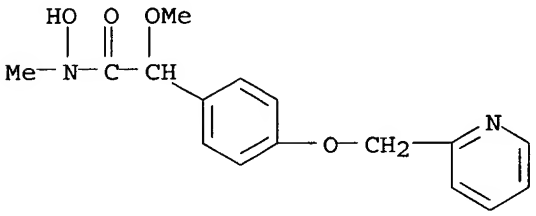
IT 108-85-0, Cyclohexyl bromide 137-43-9, Bromocyclopentane 2404-35-5, Cycloheptyl bromide 2550-36-9, (Bromomethyl)cyclohexane
RL: RCT (Reactant); RACT (Reactant or reagent)
(α-alkylation by, in preparation of (hetero)aryl-containing hydroxyamides as lipoxygenase inhibitors)

IT **158606-81-6P 158606-83-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as lipoxygenase inhibitor)

RN 158606-81-6 HCAPLUS
CN Benzeneacetamide, N-hydroxy-α-methoxy-N-methyl-4-(2-quinolinylmethoxy)- (9CI) (CA INDEX NAME)



RN 158606-83-8 HCAPLUS
CN Benzeneacetamide, N-hydroxy-α-methoxy-N-methyl-4-(2-pyridinylmethoxy)- (9CI) (CA INDEX NAME)



L66 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:147306 HCAPLUS
DOCUMENT NUMBER: 118:147306
TITLE: Preparation of α-oxobenzeneacetic acids and related compounds as antiischemics and antiarrhythmics
INVENTOR(S): Guthrie, Robert William; Heathers, Guy Phillip; Higgins, Alan John; Kachensky, David Francis; Kierstead, Richard Wightmann; LeMahieu, Ronald Andrew; Mullin, John Guilfoyle, Jr.; Tilley, Jefferson Wright
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., AG, Switz.
SOURCE: Eur. Pat. Appl., 166 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
US 5344843	A	19940906	US 1992-850620	19920313
PRIORITY APPLN. INFO.:			US 1991-698014 A	19910509
			US 1992-850620 A	19920313

OTHER SOURCE(S): MARPAT 118:147306
ED Entered STN: 13 Apr 1993
AB Title compds. I [R1 = OH, OR3, NR4R5; 1 of R4, R5 = H, C1-7 (hydroxy)alkyl and the other = H, OH, C1-7 alkyl, C1-7 alkoxy; R3 = (CH2CH2O)mH, CH2CHOHCH2OH, 2,2-dimethyl-1,3-dioxolan-4-yl, CH2CH2NH2, etc.; m = 1-4; R2, R2' = H, C1-7 alkyl, aryl-C1-7 alkyl, C1-7 alkoxy, OH, NH2, C1-7 alkylamino, cyano, halo, SH, etc.; A = bond, O, NR7, S, SO, SO2, C.tplbond.C, CH:CH, CH2CH, NR8CO, CONR9; R7 = H, C1-7 alkyl, acyl; R8,R9 = H, C1-7 alkyl; n = 0-10; B = bond, groups defined for A, CO, CS, (OCH2CH2)mO, etc.; Z = O, S, CR2:CR2', N:CR2, CR2:N, NR11; R11 = H, C1-7 alkyl; XY = O, S, :NOH, alkoxyimino, alkenyloxyimino, hydrazono, etc., or individually 1 of X and Y = halo and the other = H, halo, C1-7 alkyl, aryl-C1-7 alkyl; other possibilities for X and Y; Q = cycloalkyl, aryl, heterocyclyl; with provisos] were prepared as drugs to prevent injury to ischemic tissue and arrhythmias during and after a myocardial infarction. Thus, Me 4-hydroxy-α-oxobenzeneacetate in DMF containing NaH was O-alkylated by Ph(CH2)3Br and the resultant product was hydrolyzed by NaOH in MeOH to give title compound II. II had IC50 of 0.5 μM against carnitine acyltransferase 1 in mitochondria. Over 200 I were prepared Capsules containing I were also prepared
IC ICM C07C059-90
ICS A61K031-19; C07C065-40
CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
ST oxobenzeneacetic acid prepn antiischemic antiarrhythmic; myocardial infarction treatment oxobenzeneacetic acid
IT Ischemia
(treatment of, oxobenzeneacetic acids and related compds. for)
IT Antiarrhythmics
(α-oxobenzeneacetic acids and related compds.)
IT Heart, disease
(infarction, treatment of, oxobenzeneacetic acids and related compds. for)
IT 39386-49-7
RL: USES (Uses)
(inhibitors, α-oxobenzeneacetic acids and related compds.)
IT 145795-03-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 145794-08-7P 145794-09-8P 145794-10-1P 145794-12-3P 145794-14-5P
145794-16-7P 145794-20-3P 145794-21-4P 145794-23-6P 145794-25-8P
145794-27-0P 145794-29-2P 145794-31-6P 145794-33-8P 145794-35-0P
145794-37-2P 145794-39-4P 145794-41-8P 145794-43-0P 145794-45-2P
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145794-57-6P 145794-59-8P 145794-61-2P 145794-63-4P 145794-65-6P
145794-67-8P 145794-69-0P 145794-71-4P 145794-73-6P 145794-75-8P
145794-77-0P 145794-79-2P 145794-80-5P 145794-82-7P 145794-84-9P
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145794-96-3P 145794-98-5P 145794-99-6P 145795-01-3P 145795-02-4P
145795-04-6P 145795-05-7P 145795-06-8P 145795-07-9P 145795-08-0P
145795-09-1P 145795-10-4P 145795-11-5P 145795-12-6P 145795-13-7P

145795-14-8P 145795-15-9P 145795-16-0P 145795-17-1P 145795-18-2P
145795-19-3P 145795-20-6P 145795-21-7P 145795-22-8P 145795-23-9P
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145795-34-2P 145795-35-3P 145795-36-4P 145795-37-5P 145795-38-6P
145795-39-7P 145795-40-0P 145795-41-1P 145795-42-2P 145795-43-3P
145795-44-4P 145795-45-5P 145795-46-6P 145795-47-7P 145795-48-8P
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145795-54-6P 145795-55-7P 145795-56-8P 145795-57-9P 145795-58-0P
145795-59-1P 145795-60-4P 145795-61-5P 145795-62-6P 145795-63-7P
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145795-84-2P 145795-85-3P 145795-86-4P 145795-87-5P 145795-88-6P
145795-89-7P 145795-90-0P 145795-91-1P 145795-92-2P 145795-93-3P
145795-94-4P 145795-95-5P **145795-96-6P** 145795-97-7P
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145796-08-3P 145796-09-4P 145796-10-7P 145796-11-8P 145796-12-9P
145796-13-0P 145796-14-1P 145796-15-2P 145796-16-3P 145796-17-4P
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145796-38-9P 145796-39-0P 145796-40-3P 145796-41-4P 145796-42-5P
145796-43-6P 145796-44-7P 145796-45-8P 145796-46-9P 145796-47-0P
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146548-39-2P 146548-40-5P 146548-41-6P 146548-42-7P 146548-43-8P
146548-44-9P 146548-45-0P 146548-46-1P 146548-47-2P 146548-48-3P
146548-50-7P 146572-66-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antiischemic and antiarrhythmic)

IT 69651-48-5P 89012-04-4P 101125-34-2P 131003-09-3P 134748-95-1P
145794-07-6P 145794-11-2P 145794-13-4P 145794-15-6P 145794-17-8P
145794-18-9P 145794-19-0P 145794-22-5P 145794-24-7P 145794-26-9P
145794-28-1P 145794-30-5P 145794-32-7P 145794-34-9P 145794-36-1P
145794-38-3P 145794-40-7P 145794-42-9P 145794-44-1P 145794-46-3P
145794-48-5P 145794-50-9P 145794-52-1P 145794-54-3P 145794-56-5P
145794-58-7P 145794-60-1P 145794-62-3P 145794-64-5P 145794-66-7P
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145798-18-1P 145798-19-2P 145798-20-5P 145798-21-6P 145798-22-7P
145798-23-8P 145798-24-9P 145798-25-0P 145798-26-1P 145798-27-2P
145798-28-3P 146572-67-0P 160062-32-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for antiischemics and antiarrhythmics)

IT 56-81-5, Glycerol, reactions 74-88-4, Methyl iodide, reactions
75-16-1, Methyl magnesium bromide 75-36-5, Acetyl chloride 79-22-1,
Methyl chloroformate 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 92-44-4,
2,3-Dihydroxynaphthalene 93-20-9 96-49-1, Ethylene carbonate
100-39-0, Benzyl bromide 100-79-8, Solketal 106-89-8, Epichlorohydrin,
reactions 108-00-9, N,N-Dimethylethylenediamine 108-01-0 108-95-2,
Phenol, reactions 109-86-4 111-42-2, Diethanolamine, reactions
112-27-6, Triethylene glycol 122-99-6, 2-Phenoxyethanol 124-40-3,
Dimethylamine, reactions 124-63-0, Methanesulfonyl chloride 141-43-5,
Ethanolamine, reactions 358-23-6, Triflic anhydride 403-14-5
460-00-4, 4-Fluorobromobenzene 544-92-3, Cuprous cyanide 563-41-7,
Semicarbazide hydrochloride 588-63-6 589-10-6, β-Bromophenetole
593-56-6, Methoxylamine hydrochloride 593-77-1, N-Methylhydroxylamine
613-54-7, Bromomethyl 2-naphthyl ketone 637-59-2, 3-Bromo-1-
phenylpropane 691-64-5 769-39-1, 2,3,5,6-Tetrafluorophenol 875-59-2
876-02-8 920-39-8, Isopropylmagnesium bromide 939-26-4,
2-Bromomethylnaphthalene 1137-41-3, p-Aminobenzophenone 1200-03-9
1590-22-3 1817-88-5 1940-28-9, 4-Bromo-3,5-dichlorophenol 2243-83-6,
2-Naphthoyl chloride 2450-71-7, Propargylamine 2478-38-8 2605-67-6
2687-43-6, O-Benzylhydroxylamine hydrochloride 2892-29-7 2967-54-6,
3,5-Difluoro-4-hydroxybenzonitrile 3332-29-4 3355-31-5 3747-74-8,
2-Chloromethylquinoline hydrochloride 3814-20-8 4225-92-7 4755-77-5
5856-77-9, 2,2-Dimethylbutyryl chloride 6089-04-9 6315-52-2
6322-56-1 6707-01-3, Chloromethoxybenzene 13246-14-5 15573-67-8
16839-97-7, 2-Methoxythiophene 17044-70-1 18162-48-6,
tert-Butyldimethylsilyl chloride 20009-28-3 20020-27-3 21087-29-6
21886-62-4 22118-09-8, Bromoacetyl chloride 22921-72-8 23287-26-5
23314-24-1 24484-55-7 27650-59-5 31076-84-3, 4-Acetylbenzoyl
chloride 32462-30-9 34604-52-9 36754-60-6, 2-Chloromethylbenzofuran
37595-74-7 38250-16-7 38945-21-0 39199-93-4 40299-87-4
40786-20-7 40926-77-0 41656-75-1 51795-97-2 53542-78-2
54537-30-3 60753-14-2, 3-Pyridinebutanol 61236-14-4 62001-72-3
63649-88-7 63649-90-1 63650-21-5 64957-86-4 65512-08-5
66340-55-4 68301-59-7 69189-03-3 76469-33-5 77923-27-4
86902-13-8 87271-22-5 87723-22-6 91540-82-8 93957-49-4
98619-07-9 98793-02-3 99690-59-2 110754-02-4 113272-40-5
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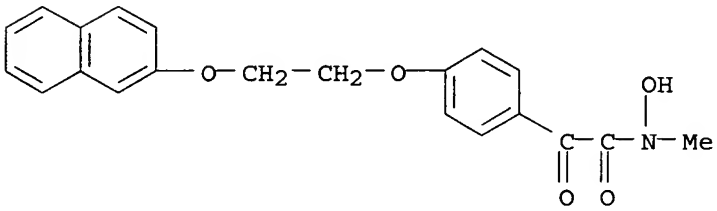
145798-56-7 145798-57-8 145798-58-9 145798-59-0 145798-60-3
145798-61-4 145798-62-5 145798-63-6 145798-64-7 145798-65-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of antiischemics and antiarrhythmics)

IT **145795-96-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antiischemic and antiarrhythmic)

RN 145795-96-6 HCAPLUS
CN Benzeneacetamide, N-hydroxy-N-methyl-4-[2-(2-naphthalenyloxy)ethoxy]-α-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:611677 HCAPLUS
DOCUMENT NUMBER: 117:211677
TITLE: Synthesis, chemical, and biological properties of vinylogous hydroxamic acids: dual inhibitors of 5-lipoxygenase and IL-1 biosynthesis
AUTHOR(S): Wright, Stephen W.; Harris, Richard R.; Kerr, Janet S.; Green, Alicia M.; Pinto, Donald J.; Bruin, Elaine M.; Collins, Robert J.; Dorow, Roberta L.; Mantegna, Lisa R.; et al.
CORPORATE SOURCE: Inflammatory Dis. Res., Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0353, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(22), 4061-8
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 117:211677
ED Entered STN: 28 Nov 1992
AB Vinylogous hydroxamic acids, 3-(N-hydroxy-N-alkylamino)-2-propen-1-ones (VHAs), were prepared as antiinflammatory agents. The synthesis, chemical properties, and in vitro biol. activities of these relatively unexplored compds. are described. The VHAs were prepared by condensation of the appropriate N-substituted hydroxylamine with any of three reagents: a 1,3-dicarbonyl compound, a vinylogous amide, or an alkynone. The VHAs exist as one or more tautomers in solution with the relative proportions of each being dependent upon the structure of the VHA, solvent, and pH. VHAs undergo some of the typical reactions of hydroxamic acids as well as those of vinylogous amides. VHAs are active as inhibitors of 5-lipoxygenase and of IL-1 biosynthesis in vitro, which do not inhibit other enzymes of the arachidonic acid cascade. They have been shown by ESR studies to bring about inhibition of soybean type 1 15-lipoxygenase by reduction of the active site iron.

CC 21-2 (General Organic Chemistry)
Section cross-reference(s): 1
ST vinylogous hydroxamic acid prepn antiinflammatory; lipoxygenase inhibition vinylogous hydroxamic acid; Il1 biosynthesis inhibition vinylogous hydroxamic acid; tautomer vinylogous hydroxamic acid
IT Tautomerism and Tautomers
(of vinylogous hydroxamic acids)
IT Inflammation inhibitors
(vinylogous hydroxamic acids)
IT Lymphokines and Cytokines
RL: RCT (Reactant); RACT (Reactant or reagent)
(interleukin 1β, inhibition of biosynthesis of, by vinylogous hydroxamic acids)
IT 403-42-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of)
IT 88-15-3, 2-Acetylthiophene 100-06-1 100-19-6 120-44-5, 1,2-Di-p-anisylethanone 451-40-1, 1,2-Diphenylethanone 765-43-5, Acetylcyclopropane 1122-54-9, 4-Acetylpyridine 1192-62-7, 2-Acetylfuran 1468-83-3, 3-Acetylthiophene 4495-66-3 22720-75-8 30071-93-3 54696-05-8, 4-Benzyloxyacetophenone 87483-29-2 143620-85-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with DMF acetal)
IT 4637-24-5, Dimethylformamide dimethyl acetal
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with acetylfuran)
IT 67860-32-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with benzylhydroxylamine)
IT 100-65-2, N-Phenylhydroxylamine 593-77-1, N-Methylhydroxylamine 622-30-0, N-Benzylhydroxylamine 2211-64-5, N-Cyclohexylhydroxylamine 3217-93-4 7803-49-8, Hydroxylamine, reactions 134796-86-4 143620-84-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with propanedione derivative)
IT 26228-72-8, N-Decylhydroxylamine 106328-99-8 111525-02-1 143620-86-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with propenone derivative)
IT 623-91-6, Diethyl fumarate 941-69-5, N-Phenylmaleimide
RL: RCT (Reactant); RACT (Reactant or reagent)
(cycloaddn. reaction of, with hydroxylaminopropenone derivative)
IT 99-91-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(formylation and condensation of, with DMF acetal)
IT 93-08-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(formylation and reaction with hydroxylamine derivative)
IT 75-97-8, tert-Butyl methyl ketone 92-91-1 529-34-0, 1-Tetralone 579-74-8 2040-05-3 2642-63-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(formylation of)
IT 9029-60-1
RL: PROC (Process)
(inhibition of, by vinylogous hydroxamic acids)
IT 143620-64-8P 143620-65-9P 143620-67-1P 143620-73-9P 143620-89-7P 143620-90-0P 143621-01-6P 143621-02-7P 143621-03-8P 143621-04-9P 143621-08-3P 143621-09-4P 143621-10-7P 143621-12-9P 143621-13-0P 143621-14-1P 143621-16-3P 143621-17-4P 143621-19-6P 143621-20-9P 143621-21-0P 143621-22-1P 143621-23-2P 143621-24-3P 143621-25-4P

143621-26-5P 143621-30-1P 143631-85-0P 143631-86-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and inhibition by, of 5-lipoxygenase and IL-1 biosynthesis)

IT 143620-66-0P 143620-68-2P 143620-69-3P 143620-70-6P 143620-71-7P
143620-72-8P 143620-74-0P 143620-75-1P 143620-76-2P 143620-91-1P
143620-92-2P 143620-94-4P 143620-95-5P 143620-96-6P 143620-97-7P
143620-98-8P 143620-99-9P 143621-00-5P 143621-05-0P 143621-06-1P
143621-07-2P 143621-11-8P 143621-15-2P 143621-18-5P 143621-27-6P
143621-28-7P 143621-29-8P 143631-83-8P 143631-87-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and inhibition of 5'-lipoxygenase by)

IT 56856-73-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with benzylhydroxylamine)

IT 109482-86-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with hydroxylamine derivative)

IT 143620-77-3P 143620-78-4P 143620-79-5P 143620-80-8P 143620-81-9P
143620-82-0P 143620-83-1P 143631-84-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

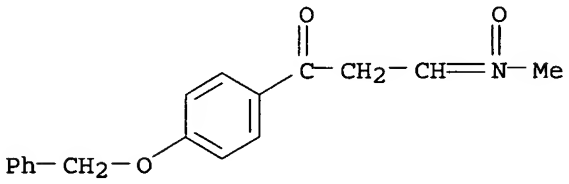
IT 143620-93-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, reactions, tautomerism, and inhibition by, of 5'-lipoxygenase and IL-1 biosynthesis)

IT 142556-94-3P **143620-87-5P** 143620-88-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, tautomerism, and inhibition by, of 5'-lipoxygenase and IL-1 biosynthesis)

IT 922-67-8, Methyl propiolate
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with benzyloxybenzylhydroxylamine)

IT **143620-87-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, tautomerism, and inhibition by, of 5'-lipoxygenase and IL-1 biosynthesis)

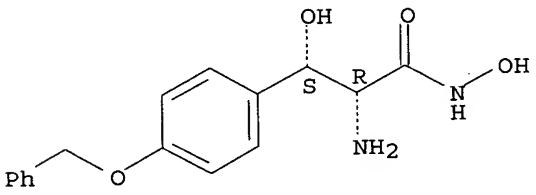
RN 143620-87-5 HCAPLUS
CN 1-Propanone, 3-(methyloxidoimino)-1-[4-(phenylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



L66 ANSWER 9 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1968:12886 HCAPLUS
DOCUMENT NUMBER: 68:12886
TITLE: Synthesis of trans-5-(p-hydroxyphenyl)-4-amino-3-isoxazolidone as an inhibitor of enzymic conversions involving tyrosine
AUTHOR(S): Khomutov, R. M.; Severin, E. S.; Gulyaev, N. N.

CORPORATE SOURCE: Inst. Molek. Biol., Moscow, USSR
SOURCE: Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1967), (7), 1622-4
CODEN: IASKA6; ISSN: 0002-3353
DOCUMENT TYPE: Journal
LANGUAGE: Russian
ED Entered STN: 12 May 1984
AB Threo-β-p-benzyloxyphenylserine and 1 mole HCl in MeOH cooled to 0° and kept overnight gave the Me ester HCl, m. 165-6°, which treated with MeONa in MeOH, then with HONH2 solution in MeOH at -5°, then 20° overnight, gave 66% p-PhCH2OC6H4CH(OH)CH(NH2)CONHOH, threo isomer, decomposed 150-1°, which hydrogenated over Pd to 80% p-hydrogenated analog, decomposed 155-6°. This in the presence of concentrated H2SO4 at -15° formed trans-5-p-hydroxyphenyl-4-amino-3-isoxazolidone, 26%, decomposed 135-40°. The substance is an inhibitor of enzymic changes of tyrosine.
CC 28 (Heterocyclic Compounds (More Than One Hetero Atom))
ST INHIBITOR ENZYMIC CHANGES TYROSINE; ISOXALIDONES AMINO; AMINO ISOXALIDONES; TYROSINE ENZYMIC CHANGES INHIBITOR
IT 60-18-4, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, inhibition by trans-4-amino-5-(p-hydroxyphenyl)-3-isoxazolidinone)
IT **16444-07-8P** 16444-08-9P 16446-49-4P 16446-50-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT **16444-07-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 16444-07-8 HCAPLUS
CN Hydracrylohydroxamic acid, 2-amino-3-[p-(benzyloxy)phenyl]-, threo- (8CI) (CA INDEX NAME)

Relative stereochemistry.



L66 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1945:1769 HCAPLUS
DOCUMENT NUMBER: 39:1769
ORIGINAL REFERENCE NO.: 39:286a-g
TITLE: Synthetic norephedrine and isoquinoline derivatives
AUTHOR(S): v. Fodor, Gabor
SOURCE: Ber. (1943), 76B, 1216-23
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 39:1769
ED Entered STN: 16 Dec 2001
AB cf. C. A. 38, 2045.7. Eugenol (200 g.) in 600 cc. EtOH, treated with 70 g. KOH in 70 cc. H2O and then with 160 g. PhCH2Cl, shaken at 20°

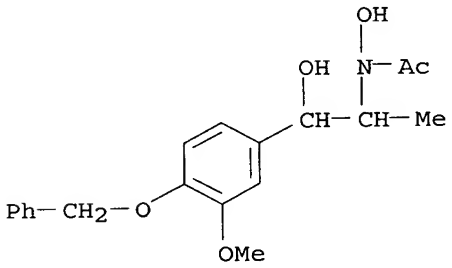
and finally heated 2 h. at 100°, gives eugenol benzyl ether; solution in 1.3 l. EtOH, addition of 500 g. powdered KOH and heating 17-20 h. give 84% of
isoeugenol benzyl ether (I). I results in 91% yield from 100 g. isoeugenol in 300 cc. EtOH, 35 g. KOH in 50 cc. H2O and 80 g. PhCH2Cl on boiling 3.5 h. I (100 g.) in 1 l. ether and 280 g. NaNO2 in 150 cc. H2O, treated during 5-6 h. with 1 l. 20% H2SO4 and allowed to stand overnight, give 77% of the ψ-nitrosite (II), m. 125-6° (decomposition). A suspension of 33 g. II in 90 cc. H2O at 8-10°, treated with 2 drops concentrated H2SO4 (temperature not above 20°), stirred for 15 min. and poured into 1 l. H2O, gives 80% of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-nitropropane (III), m. 130°. II or III with KOH in 75% EtOH gives β-nitroisoeugenol benzyl ether, canary-yellow, m. 92°. Reduction of 14.5 g. III in 100 cc. AcOH and 200 cc. EtOH at 50-60° with a Pb cathode (0.07 amp./sq. cm.), 10 cc. concentrated HCl being added during the reduction, gives 32% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-acetamidopropane (IV), m. 138° (purified by extraction of the AcOEt solution with N NaOH), and 38% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-(N-acetylhydroxyamino)propane (V), m. 144-7°; V reduces Fehling solution at room temperature and gives a deep violet color with FeCl3. Reduction of
III in AcOH-EtOH with a Hg cathode for 1.5 h. gives 60% of IV. IV (1.65 g.) and 1.1 cc. 5 N EtOH-HCl, heated at 30-40°, gives 1.5 g. of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-aminopropane-HCl (VI), m. 193°; 1 g. V in 20 cc. H2O and 4 cc. N NaOH gives 0.41 g. of IV. IV (4.82 g.) in 29 cc. N HCl and 18 cc. H2O, heated 3 h. on the water bath and treated dropwise with 43 cc. N NaOH, gives 42% of 1-(3-methoxy-4-benzyloxyphenyl)-1-hydroxy-2-aminopropane[3-methoxy-4-benzyloxynorephedrine] (VII), m. 129°; HCl salt (VIII), m. 210°. VIII also results in 3.2-g. yield by treating 6.58 g. of IV in 20 cc. EtOH with 4.8 cc. 4.2 N EtOH-HCl and then with 35 cc. H2O and refluxing 6 h. VII (1.15 g.) in 20 cc. MeOH, shaken with H (Pd-charcoal) for 10 min., gives 0.8 g. of 3-methoxy-4-hydroxynorephedrine (IX), m. 149-50°; 2.5 g. VIII similarly gives 1.66 g. of the HCl salt of IX, m. 206°. IX and CH2N2 give 1-(3,4-dimethoxyphenyl)-2-amino-1-propanol, m. 126-8° (Pfeiffer, C. A. 34, 2383.3). V (0.7 g.) in 10 cc. EtOH and 1 cc. 6 N EtOH-HCl, allowed to stand 2 h., gives 0.57 g. of 1-(3-methoxy-4-benzyloxyphenyl)-1-acetoxy-2-hydroxy-aminopropane-HCl, m. 163°; with alkali this yields VI. IV (1.65 g.) in 17 cc. CHCl3 and 1.5 cc. POCl2, refluxed 3 h., gives 69% of 1,3-dimethyl-6-methoxy-7-benzyloxy-isoquinoline (X), m. 150°; HCl salt, m. 245°; nitrate, m. 215° (decomposition). Catalytic reduction of X in PhMeEtOH at room temperature gives 1,3-dimethyl-6-methoxy-7-hydroxyisoquinoline (XI), m. 175°; HCl salt, m. 265° (decomposition); CH2N2 gives the 6,7-di-MeO derivative, m. 119-20°. XI and 3,4-(MeO)2C6H3CH2Cl with aqueous KOH in EtOH give 33% of 1,3-dimethyl-6-methoxy-7-(3,4-dimethoxybenzyloxy)isoquinoline, m. 180-1°.

CC 10 (Organic Chemistry)

IT 7-Isoquinolinol, 6-methoxy-1,3-dimethyl-
Acetamide, N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]-
Hydroxylamine, N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]-, acetate-HCl
Norephedrine, 4-(benzyloxy)-N-hydroxy-3-methoxy-, α-acetate-HCl
Norephedrine, 4-hydroxy-3-methoxy-
Norephedrine, 4-hydroxy-3-methoxy-, -HCl
Norephedrine, N-acetyl-4-(benzyloxy)-3-methoxy-
Norephedrine, N-acetyl-4-(benzyloxy)-N-hydroxy-3-methoxy-

IT Norephedrine, 4-(benzyloxy)-3-methoxy-
(and derivs.)

IT Isoquinoline, 7-(benzyloxy)-6-methoxy-1,3-dimethyl-
(and salts)
IT 119-65-3, Isoquinoline 14838-15-4, Norephedrine
(derivs.)
IT 120-11-6, Benzene, 1-(benzyloxy)-2-methoxy-4-propenyl- 57371-42-3, Benzene, 4-allyl-1-(benzyloxy)-2-methoxy- 321125-48-8, Benzene, 1-(benzyloxy)-2-methoxy-4-(2-nitropropenyl)- 749873-38-9, Benzene, 1-(benzyloxy)-2-methoxy-4-(2-nitro-1-nitrosopropyl)- 850857-65-7, 7-Isoquinolinol, 6-methoxy-1,3-dimethyl-, -HCl 850858-37-6, Isoquinoline, 6-methoxy-1,3-dimethyl-7-veratryloxy- 855273-11-9, Benzyl alcohol, 4-(benzyloxy)-3-methoxy-α-1-nitroethyl-, acetate 855273-17-5, Benzyl alcohol, 4-(benzyloxy)-α-(1-hydroxaminoethyl)-3-methoxy-, α-acetate-HCl **855883-23-7**, Hydroxylamine, N-acetyl-N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]- **855883-23-7**, Acetamide, N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]-N-hydroxy-
(preparation of)
IT **855883-23-7**, Hydroxylamine, N-acetyl-N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]-
(preparation of)
RN 855883-23-7 HCAPLUS
CN Acetamide, N-[4-(benzyloxy)-β-hydroxy-3-methoxy-α-methylphenethyl]-N-hydroxy- (4CI) (CA INDEX NAME)



=> d ibib ab hitstr l66 11-22
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CONTINUE? (Y)/N:y

L66 ANSWER 11 OF 26 USPATFULL on STN DUPLICATE 2
ACCESSION NUMBER: 2004:300230 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
Borstel, Reid W. von, Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004236100	A1	20041125
	US 6858602	B2	20050222
APPLICATION INFO.:	US 2003-684660	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

NUMBER DATE

PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878	
NUMBER OF CLAIMS:	9	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	4283	

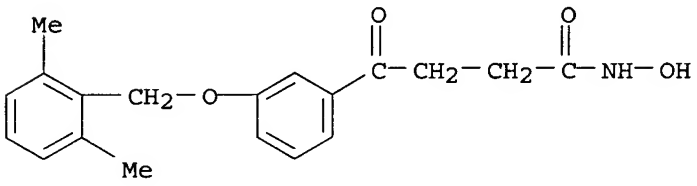
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 12 OF 26 USPATFULL on STN DUPLICATE 3

ACCESSION NUMBER:	2004:127601 USPATFULL		
TITLE:	Compounds for the treatment of metabolic disorders		
INVENTOR(S):	Sharma, Shalini, Gaithersburg, MD, UNITED STATES		

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004097585	A1	20040520
	US 6916848	B2	20050712
APPLICATION INFO.:	US 2003-684730	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Page(s)
LINE COUNT:	4236

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

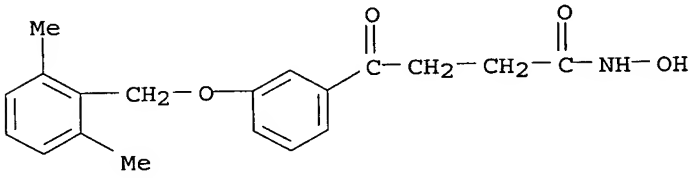
AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver

disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 13 OF 26 USPATFULL on STN DUPLICATE 4

ACCESSION NUMBER: 2004:121100 USPATFULL

TITLE: Compounds for the treatment of metabolic disorders

INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004092516	A1	20040513
	US 6946491	B2	20050920
APPLICATION INFO.:	US 2003-685183	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878

NUMBER OF CLAIMS: 21

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 2 Drawing Page(s)

LINE COUNT: 4396

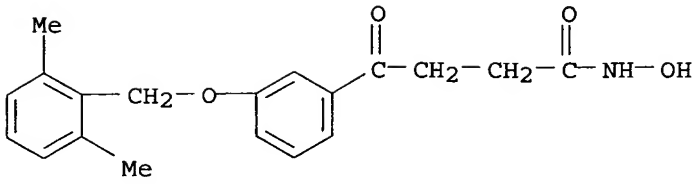
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



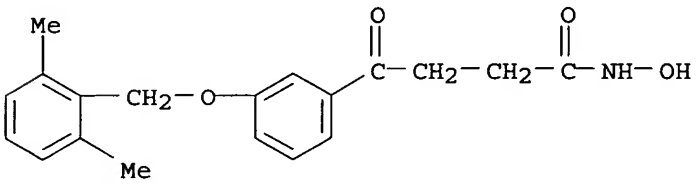
L66 ANSWER 14 OF 26 USPATFULL on STN DUPLICATE 5
ACCESSION NUMBER: 2004:102026 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004077896	A1	20040422
	US 6924314	B2	20050802
APPLICATION INFO.:	US 2003-684644	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4276
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.
IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)
RN 478162-92-4 USPATFULL
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 15 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2005:105617 USPATFULL
TITLE: Compound for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005090555	A1	20050428
APPLICATION INFO.:	US 2004-5449	A1	20041206 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-865088, filed on 10 Jun 2004, ABANDONED Continuation of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

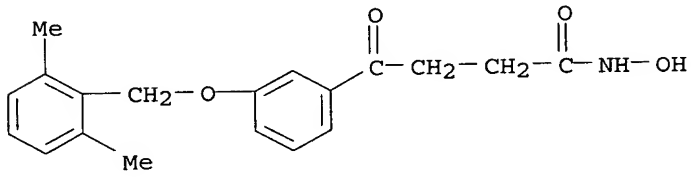
	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878, US
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4271
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



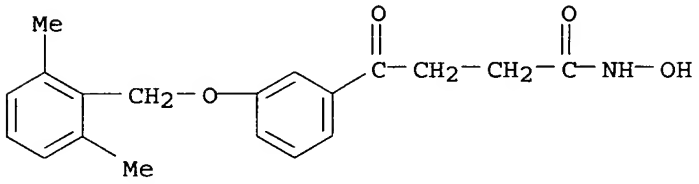
L66 ANSWER 16 OF 26 USPATFULL on STN
ACCESSION NUMBER: 2005:5009 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005004115	A1	20050106
APPLICATION INFO.:	US 2004-892950	A1	20040716 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2003-685183, filed on 14 Oct 2003, PENDING Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.
IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)
RN 478162-92-4 USPATFULL
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 17 OF 26 USPATFULL on STN
ACCESSION NUMBER: 2004:335929 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004267025	A1	20041230
APPLICATION INFO.:	US 2003-684740	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

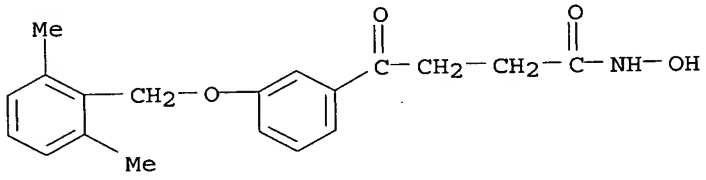
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4304
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds useful for the treatment of various metabolic disorders, such

as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 18 OF 26 USPATFULL on STN

ACCESSION NUMBER:	2004:308016 USPATFULL
TITLE:	Compounds for the treatment of metabolic disorders
INVENTOR(S):	Sharma, Shalini, Gaithersburg, MD, UNITED STATES von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004242692	A1	20041202
APPLICATION INFO.:	US 2004-865088	A1	20040610 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS:	44
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Page(s)
LINE COUNT:	4400

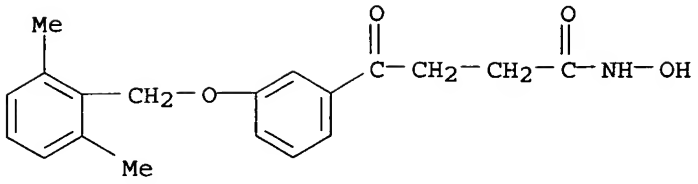
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL

CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



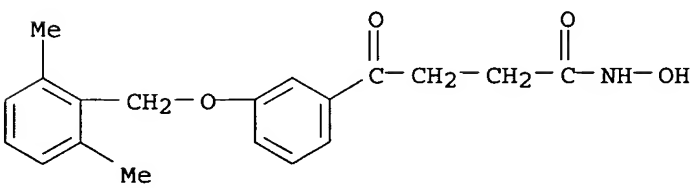
L66 ANSWER 19 OF 26 USPATFULL on STN
ACCESSION NUMBER: 2004:121102 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders
INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004092518	A1	20040513
APPLICATION INFO.:	US 2003-684735	A1	20031014 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-167839, filed on 12 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 4261
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.
IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)
RN 478162-92-4 USPATFULL
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 20 OF 26 USPATFULL on STN
ACCESSION NUMBER: 2004:83242 USPATFULL
TITLE: Hydantoin derivatives as inhibitors of matrix

metalloproteinases and/or TNF-alpha converting enzyme

INVENTOR(S): Maduskuie, Thomas P., Wilmington, DE, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004063698	A1	20040401	
APPLICATION INFO.:	US 2003-632197	A1	20030731	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-400237P	20020801 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000

NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 3217
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compounds of Formula (I): ##STR1##

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein the variables A, R.sup.1, R.sup.2, R.sup.3, R.sup.4, Z, U, X, Y, Z.sup.a, and n are defined are as defined herein, which are useful as inhibitors of matrix metalloproteinases (MMP) and/or TNF-α converting enzyme (TACE), or a combination thereof.

IT **656802-67-4P 656802-68-5P 656802-69-6P**
656802-70-9P 656802-71-0P 656802-72-1P
656802-73-2P 656802-74-3P 656802-75-4P
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656802-79-8P 656802-80-1P 656802-81-2P
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656802-85-6P 656802-86-7P 656802-87-8P
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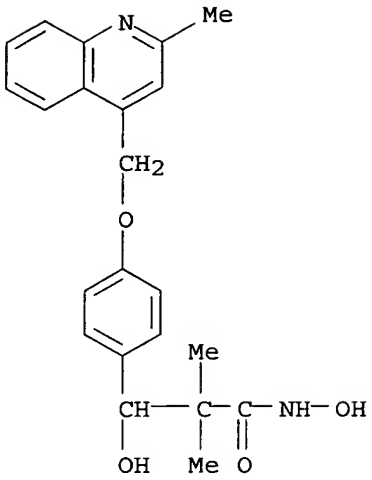
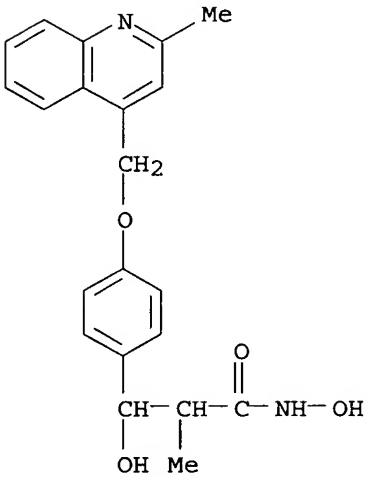
656802-91-4P 656802-92-5P 656803-05-3P
656803-06-4P 656803-07-5P 656803-08-6P
656803-09-7P 656803-11-1P 656803-12-2P
656803-14-4P 656803-16-6P 656803-18-8P
656803-20-2P 656803-22-4P 656803-24-6P
656803-26-8P 656803-28-0P 656803-30-4P
656803-32-6P 656803-33-7P 656803-35-9P
656803-36-0P
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

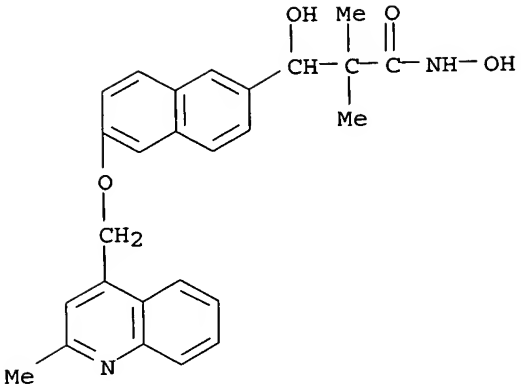
RN 656802-67-4 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α,α-dimethyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



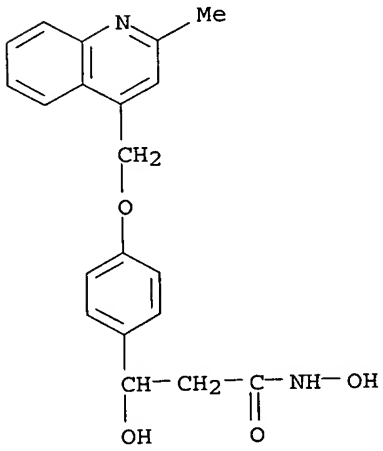
RN 656802-68-5 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



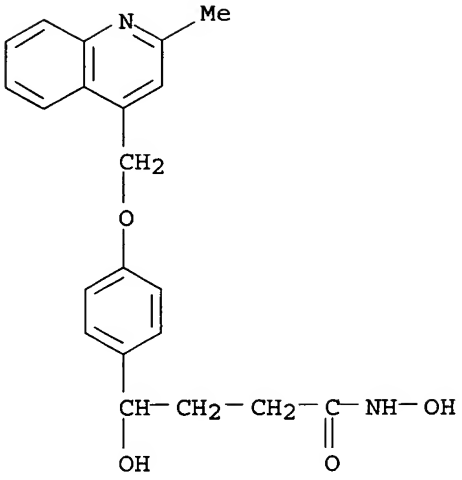
RN 656802-69-6 USPATFULL
CN 2-Naphthalenepropanamide, N,β-dihydroxy-α,α-dimethyl-6-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



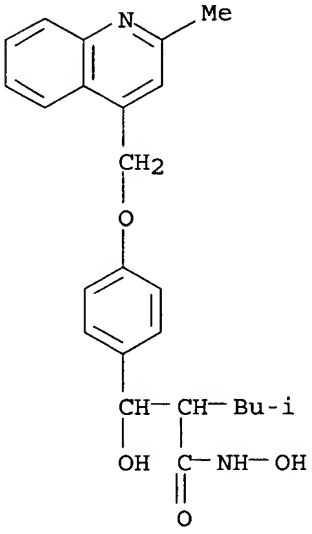
RN 656802-70-9 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



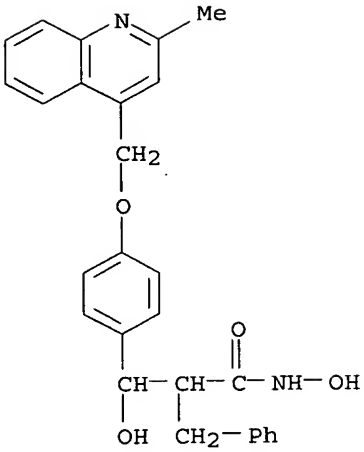
RN 656802-71-0 USPATFULL
CN Benzenebutanamide, N,γ-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-72-1 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)



RN 656802-73-2 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 656802-74-3 USPATFULL
CN 2-Furanpropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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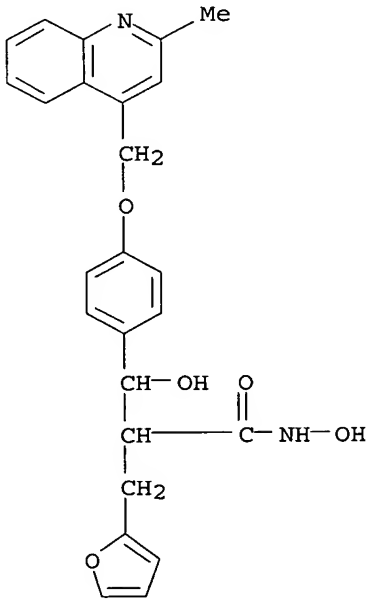

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RN 656802-75-4 USPATFULL
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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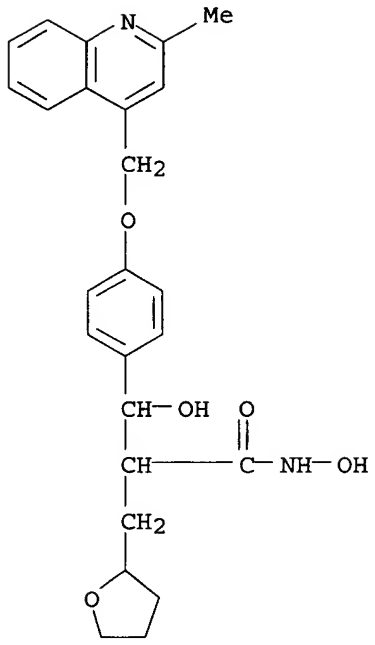

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RN 656802-76-5 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

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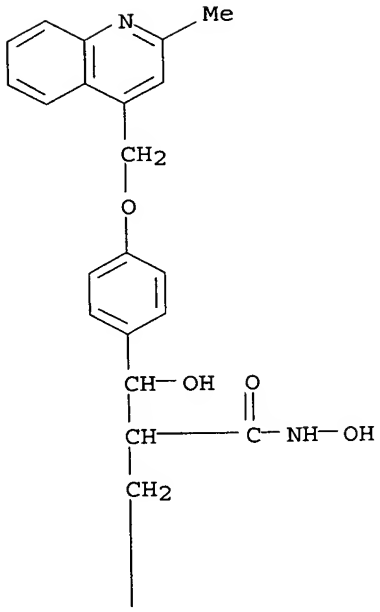
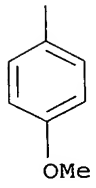


PAGE 2-A



RN 656802-77-6 USPATFULL
CN Benzenepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy- (9CI) (CA INDEX NAME)

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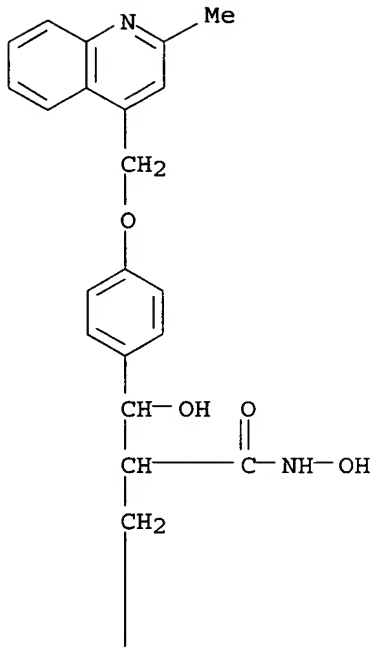

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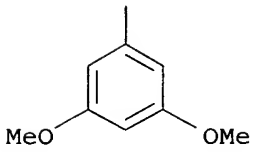
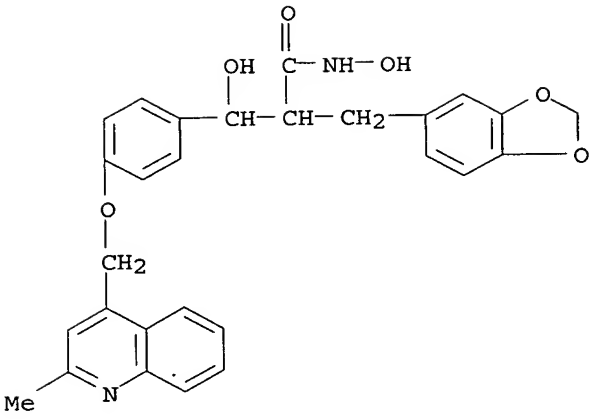


RN 656802-78-7 USPATFULL
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 656802-79-8 USPATFULL
CN 4-Pyridinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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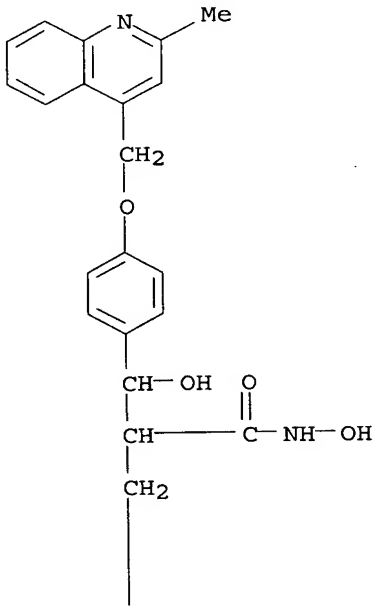

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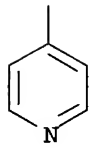
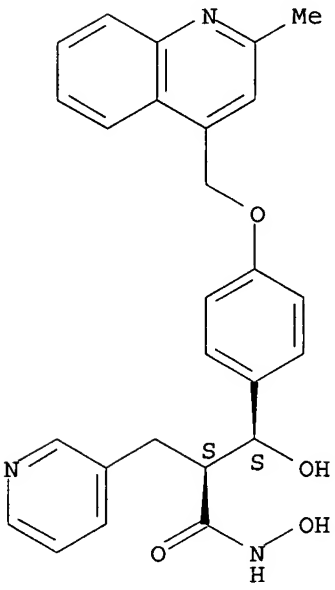


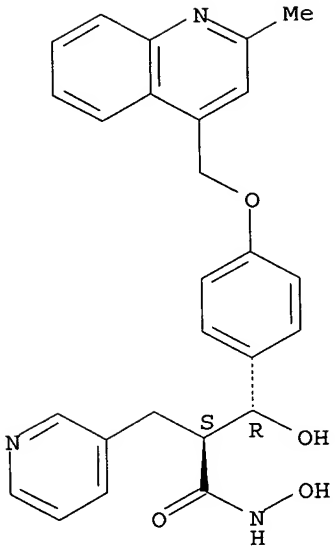
RN 656802-80-1 USPATFULL
CN 3-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656802-81-2 USPATFULL
CN 3-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656802-82-3 USPATFULL
CN 4-Morpholinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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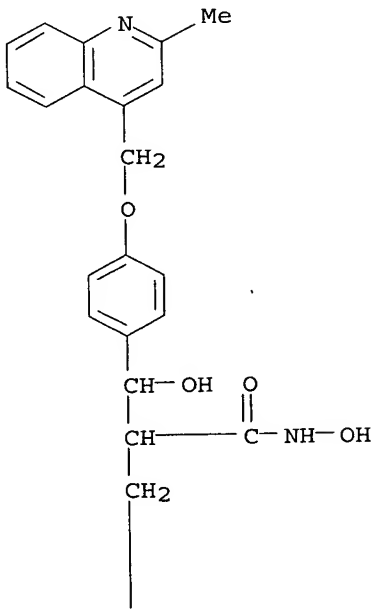

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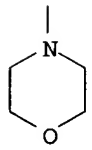

RN 656802-83-4 USPATFULL
CN 1-Piperidinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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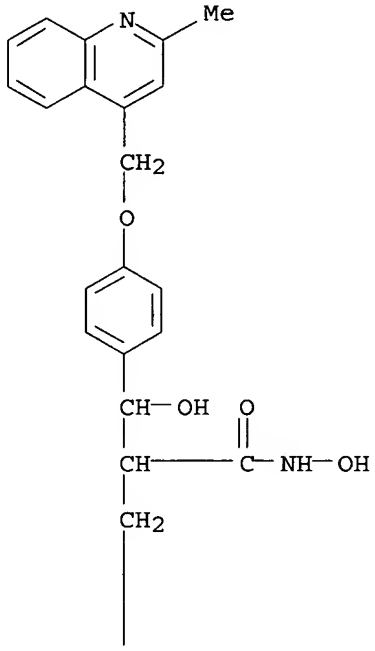

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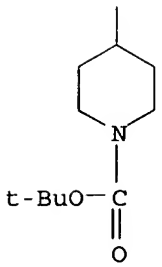

RN 656802-84-5 USPATFULL
CN 4-Piperidinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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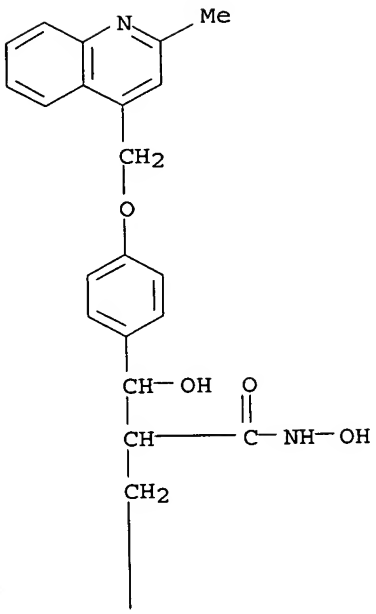

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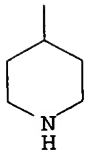

RN 656802-85-6 USPATFULL
CN 1-Piperazinecarboxylic acid, 4-[3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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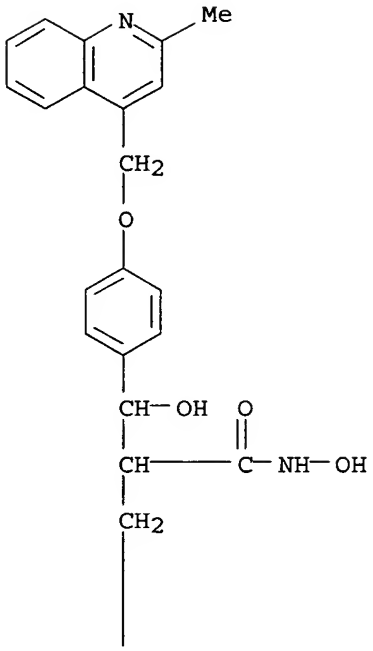

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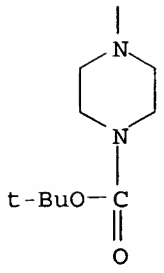

RN 656802-86-7 USPATFULL
CN 1-Piperazinepropanamide, N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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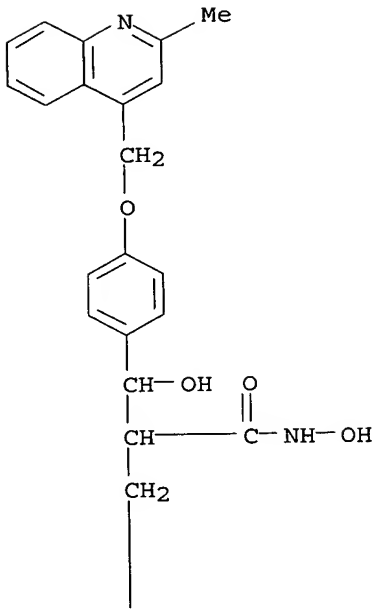

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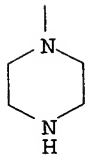
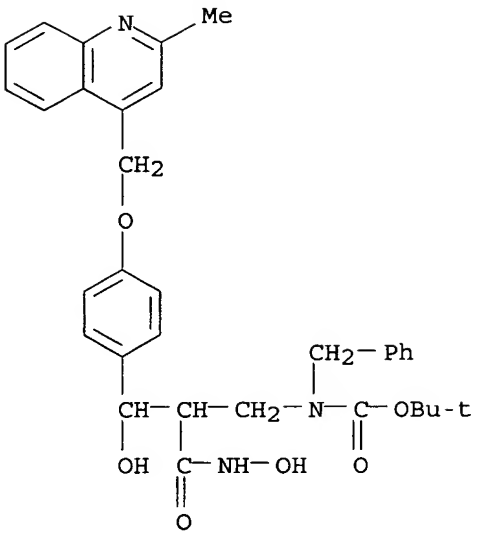
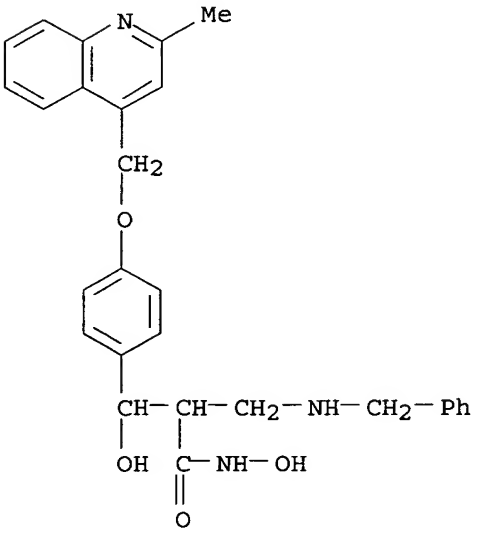


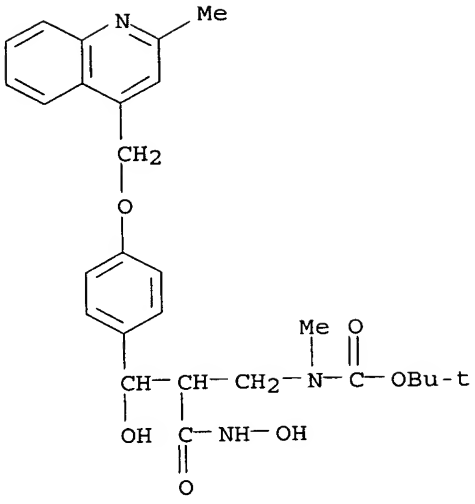
RN 656802-87-8 USPATFULL
CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl](phenylmethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



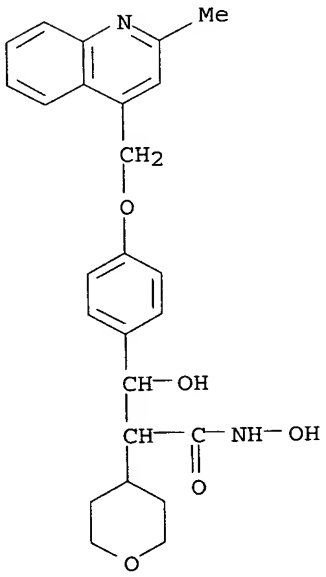
RN 656802-88-9 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-[[(phenylmethyl)amino]methyl]- (9CI) (CA INDEX NAME)



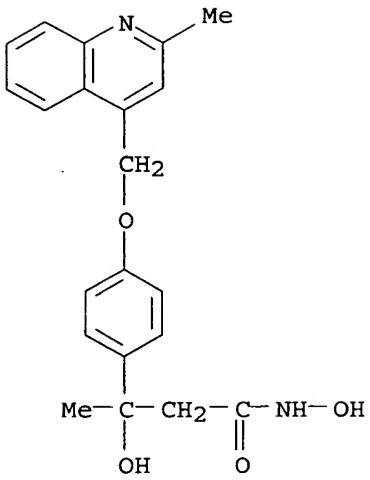
RN 656802-89-0 USPATFULL
CN Carbamic acid, [3-(hydroxyamino)-2-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



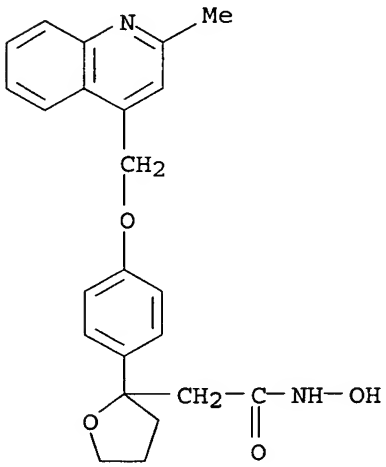
RN 656802-90-3 USPATFULL
CN 2H-Pyran-4-acetamide, tetrahydro-N-hydroxy-α-[hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 656802-91-4 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-β-methyl-4-[(2-methyl-4-quinolinyl)methoxy]- (9CI) (CA INDEX NAME)

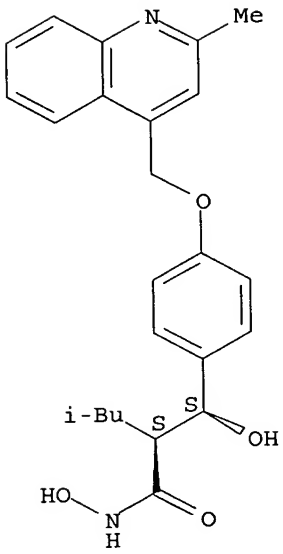


RN 656802-92-5 USPATFULL
CN 2-Furanacetamide, tetrahydro-N-hydroxy-2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



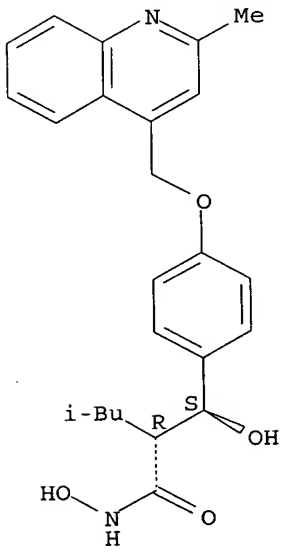
RN 656803-05-3 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



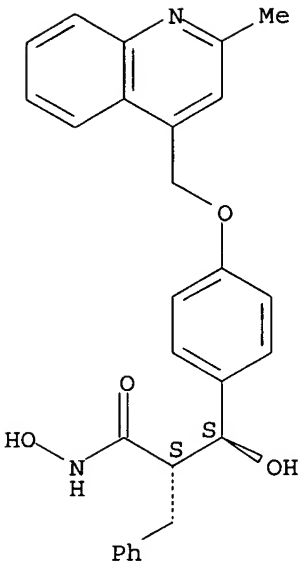
RN 656803-06-4 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-(2-methylpropyl)-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



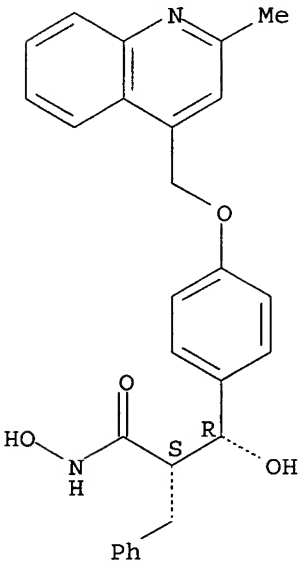
RN 656803-07-5 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



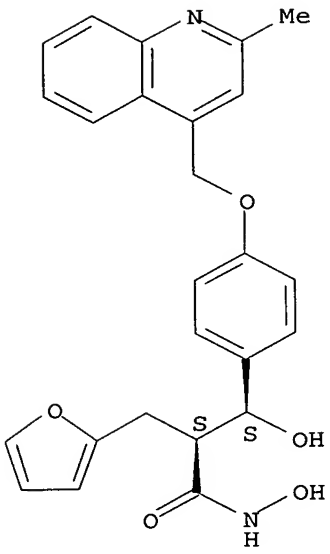
RN 656803-08-6 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-4-[(2-methyl-4-quinolinyl)methoxy]-α-(phenylmethyl)-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



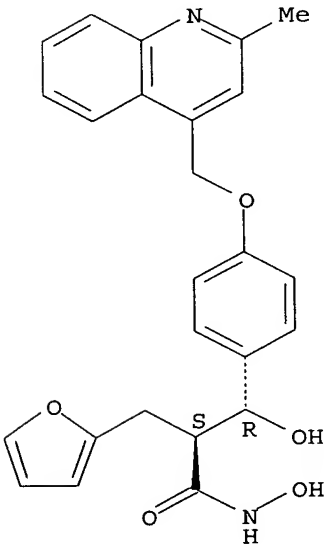
RN 656803-09-7 USPATFULL
CN 2-Furanpropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



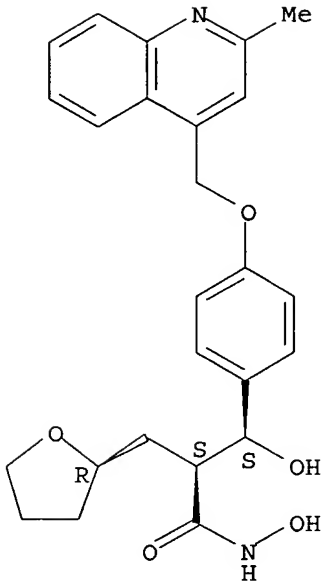
RN 656803-11-1 USPATFULL
CN 2-Furanpropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



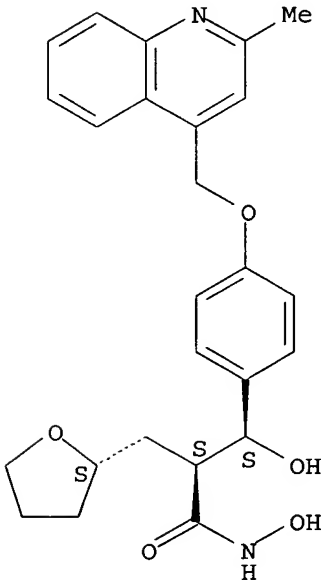
RN 656803-12-2 USPATFULL
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



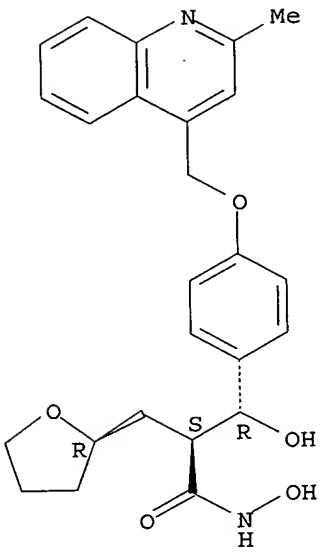
RN 656803-14-4 USPATFULL
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



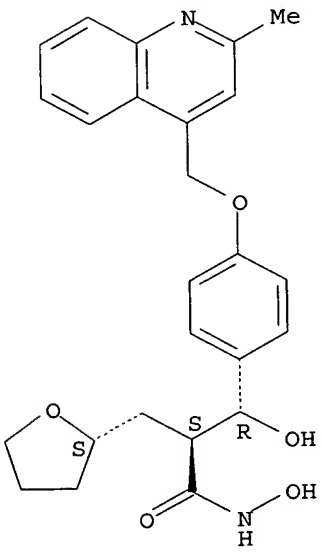
RN 656803-16-6 USPATFULL
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



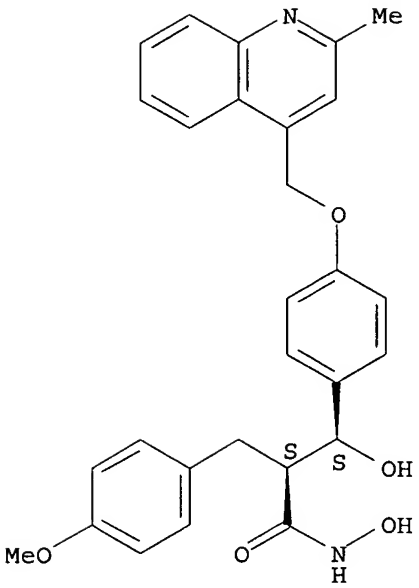
RN 656803-18-8 USPATFULL
CN 2-Furanpropanamide, tetrahydro-N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS,2S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



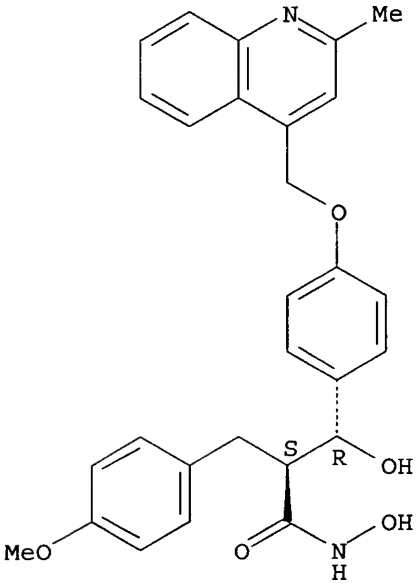
RN 656803-20-2 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



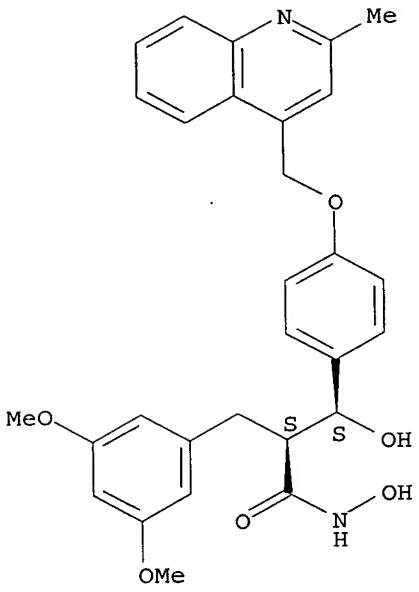
RN 656803-22-4 USPATFULL
CN Benzenepropanamide, N,β-dihydroxy-α-[(4-methoxyphenyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy]-, (αR,βS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



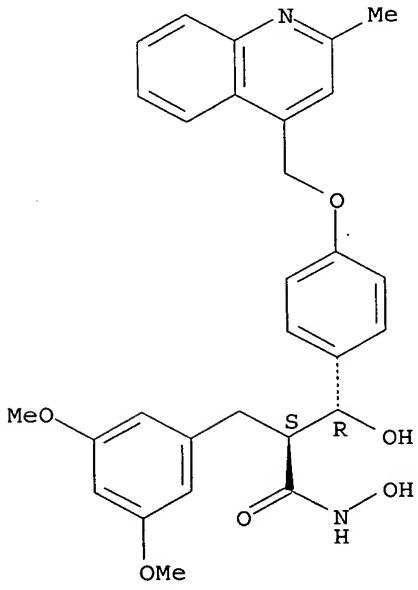
RN 656803-24-6 USPATFULL
CN Benzenepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



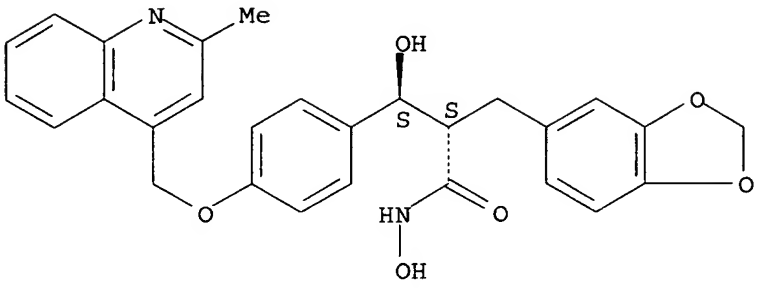
RN 656803-26-8 USPATFULL
CN Benzenepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3,5-dimethoxy-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



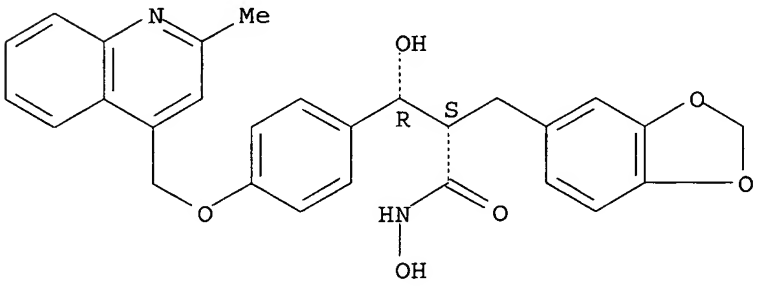
RN 656803-28-0 USPATFULL
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



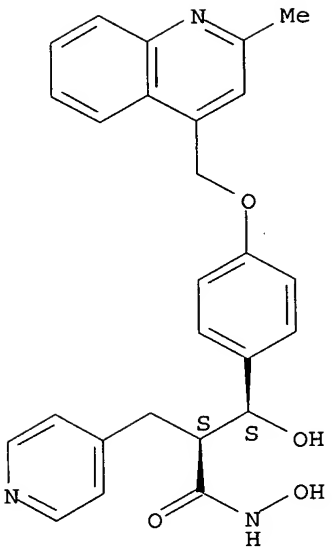
RN 656803-30-4 USPATFULL
CN 1,3-Benzodioxole-5-propanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



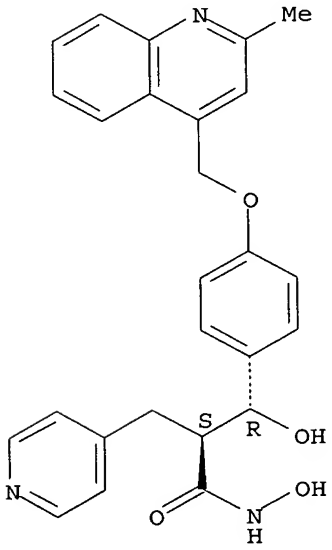
RN 656803-32-6 USPATFULL
CN 4-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



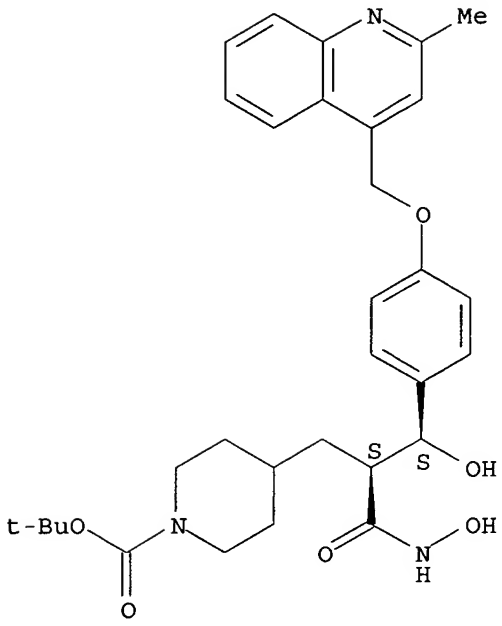
RN 656803-33-7 USPATFULL
CN 4-Pyridinepropanamide, N-hydroxy-α-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-, (αS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



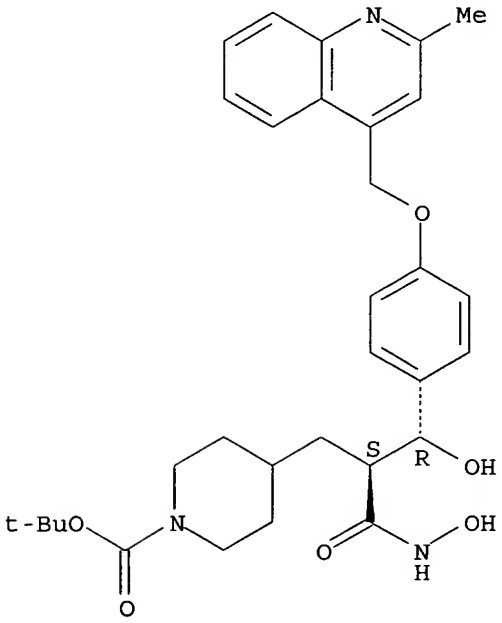
RN 656803-35-9 USPATFULL
CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(R)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 656803-36-0 USPATFULL
CN 1-Piperidinecarboxylic acid, 4-[(2R)-3-(hydroxyamino)-2-[(S)-hydroxy[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]methyl]-3-oxopropyl]-, 1,1-dimethylethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L66 ANSWER 21 OF 26 USPATFULL on STN
ACCESSION NUMBER: 2003:214464 USPATFULL
TITLE: Compounds for the treatment of metabolic disorders

INVENTOR(S): Sharma, Shalini, Gaithersburg, MD, UNITED STATES
von Borstel, Reid W., Potomac, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003149107	A1	20030807
APPLICATION INFO.:	US 2002-167839	A1	20020612 (10)

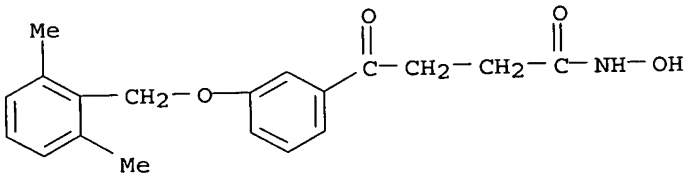
	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-297282P	20010612 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LEWIS J. KREISLER, LEGAL DEPARTMENT, 930 CLOPPER ROAD, GAITHERSBURG, MD, 20878
NUMBER OF CLAIMS: 161
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 5232
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds useful for the treatment of various metabolic disorders, such as insulin resistance syndrome, diabetes, hyperlipidemia, fatty liver disease, cachexia, obesity, atherosclerosis and arteriosclerosis, are disclosed.

IT **478162-92-4P**
(preparation of benzyloxyphenyloxobutyrates and related compds. for treatment of metabolic disorders)

RN 478162-92-4 USPATFULL
CN Benzenebutanamide, 3-[(2,6-dimethylphenyl)methoxy]-N-hydroxy-γ-oxo- (9CI) (CA INDEX NAME)



L66 ANSWER 22 OF 26 USPATFULL on STN
ACCESSION NUMBER: 96:27207 USPATFULL
TITLE: N-hydroxyureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low density lipoprotein
INVENTOR(S): Malamas, Michael S., Jamison, PA, United States
Nelson, James A., Washingtons Crossing, PA, United States
PATENT ASSIGNEE(S): American Home Products Corporation, Madison, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5504097		19960402
APPLICATION INFO.:	US 1995-423061		19950417 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1993-148603, filed on 8 Nov 1993, now patented, Pat. No. US 5459154
DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Gerstl, Robert
LEGAL REPRESENTATIVE: Boswell, Jr., R. F.
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
LINE COUNT: 1039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to compounds having 5-lipoxygenase inhibiting properties and inhibition of oxidative modification of low density lipoprotein which have the formula: ##STR1## wherein: R.sup.1 and R.sup.3 are independently hydrogen, halogen, C.sub.1 -C.sub.6 alkyl, C.sub.1 -C.sub.6 alkoxy, trifluoromethyl, or C.sub.1 -C.sub.6 trifluoroalkoxy;

R.sub.2 is hydrogen or methyl;

R.sup.4 is hydrogen, methyl or hydroxy;

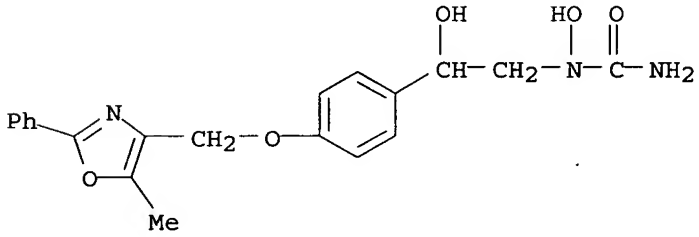
R.sup.5 is hydrogen, --NH.sub.2, C.sub.1 -C.sub.6 alkyl, aryl, aralkyl, or --N.dbd.C(CH.sub.3).sub.2 ;

X and Y are independently O or S; and n is 0 or 1; or a pharmaceutically acceptable salt thereof. Compounds which inhibit 5-lipoxygenase are useful in the treatment of diseases mediated by leukotrienes such as inflammation or bronchoconstriction. Compounds which inhibit oxidative metabolism of low density lipoprotein are useful in the inhibition of atherosclerotic plaque formation.

IT **173191-84-9P**
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173191-84-9 USPATFULL

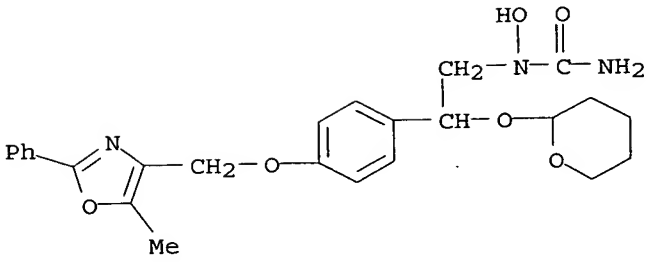
CN Urea, N-hydroxy-N-[2-hydroxy-2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]ethyl]- (9CI) (CA INDEX NAME)



IT **173192-13-7P**
(N-hydroxy-N-[4-(2-phenyloxazolyl- and -thiazolylmethoxy)benzyl]ureas as 5-lipoxygenase inhibitors and inhibitors of oxidative modification of low d. lipoprotein)

RN 173192-13-7 USPATFULL

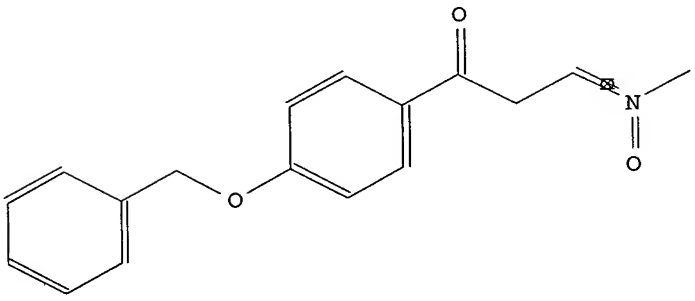
CN Urea, N-hydroxy-N-[2-[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]-2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)



=> d l66 ide 23
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y

L66 ANSWER 23 OF 26 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN):	5819891
Beilstein Pref. RN (BPR):	143620-87-5
CAS Reg. No. (RN):	**143620-87-5**
Molec. Formula (MF):	C17 H17 N O3
Molecular Weight (MW):	283.33
Lawson Number (LN):	9256, 5228, 3625
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	isocyclic
Constitution ID (CONSID):	5093914
Tautomer ID (TAUTID):	5574652
Beilstein Citation (BSO):	6-08
Entry Date (DED):	1993/05/04
Update Date (DUPD):	1994/02/18



Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
BPR	Beilstein Preferred RN	1

RN	CAS Registry Number	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
NMR	Nuclear Magnetic Resonance	3

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

=> d rx l66 23
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y

L66 ANSWER 23 OF 26 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Reaction:
RX

Reaction ID (.ID):	1897053
Reactant BRN (.RBRN):	1730792, 5815146
Reactant (.RCT):	N-methyl-hydroxylamine, 1-(4-benzyloxy-phenyl)-3-dimethylamino-propenone
Product BRN (.PBRN):	5852497, 5824062, 5819891, 5852496
Product (.PRO):	1-(4-benzyloxy-phenyl)-3-(hydroxy-methyl-amino)-propenone, 5-(4-benzyloxy-phenyl)-2-methyl-2,5-dihydro-isoxazol-5-ol, C17H17NO3, 1-(4-benzyloxy-phenyl)-3-(hydroxy-methyl-amino)-propenone
No. of React. Details (.NVAR):	1

Reaction Details:
RX

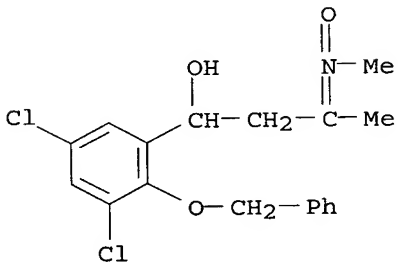
Reaction RID (.RID):	1897053.1
Reaction Classification (.CL):	Preparation
Reagent (.RGT):	p-TsOH
Solvent (.SOL):	methanol
Time (.TIM):	30 min
Temperature (.T):	20 Cel
Note(s) (.COM):	Yield given. Yields of byproduct given. Title compound not separated from byproducts

Reference(s):
1. Wright, Stephen W.; Harris, Richard R.; Kerr, Janet S.; Green, Alicia M.; Pinto, Donald J.; et al., J.Med.Chem., CODEN: JMCMAR, 35(22), <1992>, 4061-4068; BABS-5706192

=> => d iall l66 24-26
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' -
CONTINUE? (Y)/N:y

'IALL' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):all

L66 ANSWER 24 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN
Accession No. (AN): 2005:1864858 CHEMCATS
Catalog Name (CO): Interchim Intermediates
Publication Date (PD): 18 Jan 2005
Order Number (ON): 7N-908
Chemical Name (CN): Benzenemethanol, 3,5-dichloro-α-[2-(methyloxidoimino)propyl]-2-(phenylmethoxy)-
CAS Registry No. (RN): **339020-55-2**
Supplementary Term (ST): CHEMICAL LIBRARY
Structure :



PRICES

Quantity : milligram quantities, Price: contact supplier

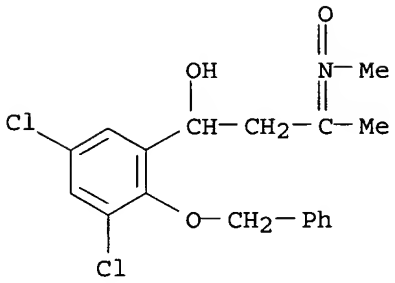
COMPANY INFORMATION

Interchim
211 bis Av J.F. Kennedy
BP 1140
Montlucon, 03103
France

Phone: (33) (0) 4 70 03 88 55
Fax: (33) (0) 4 70 03 82 60
Email: interchim@interchim.com
Web: http://www.interchim.com

L66 ANSWER 25 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN
Accession No. (AN): 2004:278246 CHEMCATS
Catalog Name (CO): Ambinter Stock Screening Collection
Publication Date (PD): 1 Jan 2004

Order Number (ON): 7N-908
Chemical Name (CN): Benzenemethanol, 3,5-dichloro-α-[2-(methyloxidoimino)propyl]-2-(phenylmethoxy)-
CAS Registry No. (RN): **339020-55-2**
Supplementary Term (ST): CHEMICAL LIBRARY
Structure :



PRICES

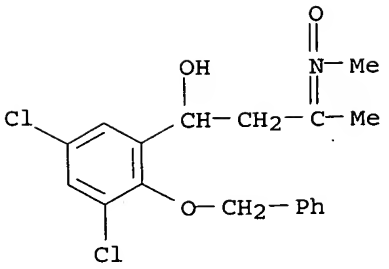
Quantity : milligram quantities, Price: contact supplier

COMPANY INFORMATION

Ambinter
46 quai Louis Bleriot
Paris, F-75016
France

Phone: (33-1) 45 24 48 60
Fax: (33-1) 45 24 62 41
Email: ambinter@compuserve.com
Web: http://www.ambinter.com

L66 ANSWER 26 OF 26 CHEMCATS COPYRIGHT 2005 ACS on STN
Accession No. (AN): 1999:148115 CHEMCATS
Catalog Name (CO): Bionet Screening Compounds
Publication Date (PD): 25 May 2005
Order Number (ON): 7N-908
Chemical Name (CN): {(E)-3-[2-(benzyloxy)-3,5-dichlorophenyl]-3-hydroxy-1-methylpropylidene}(methyl)ammoniumolate
CAS Registry No. (RN): **339020-55-2**
Supplementary Term (ST): CHEMICAL LIBRARY
Structure :



PRICES

Quantity : milligram quantities, Price: contact supplier

COMPANY INFORMATION

Bionet Research Ltd.
Highfield Industrial Estate
Camelford, Cornwall, PL32 9QZ
United Kingdom

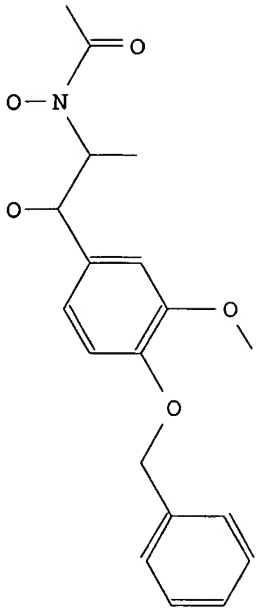
Phone: +44(0) 1840 212171
Fax: +44(0) 1840 213712
Email: enquiries@keyorganics.ltd.uk
Web: http://www.bionetresearch.co.uk

=> d que nos l63
L57 STR
L62 2 SEA FILE=BEILSTEIN SSS FUL L57
L63 1 SEA FILE=BEILSTEIN ABB=ON PLU=ON L62 NOT RN/FA

=> d ide l63
YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L63 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN):	3483237
Chemical Name (CN):	N-hydroxy-N-<2-hydroxy-2-(4-benzyloxy-3-methoxy-phenyl)-1-methyl-ethyl>-acetamide
Autonom Name (AUN):	N-<2-(4-benzyloxy-3-methoxy-phenyl)-2-hydroxy-1-methyl-ethyl>-N-hydroxy-acetamide
Molec. Formula (MF):	C19 H23 N O5
Molecular Weight (MW):	345.39
Lawson Number (LN):	16410, 5228, 1155, 289
Compound Type (CTYPE):	isocyclic
Constitution ID (CONSID):	3072587
Tautomer ID (TAUTID):	3285330
Beilstein Citation (BSO):	3-15-00-00039
Entry Date (DED):	1990/02/15
Update Date (DUPD):	1991/09/20



Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	4
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
MP	Melting Point	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

=> d l63 rx
YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L63 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Reaction:
RX

Reaction ID (.ID):	519302
Reactant BRN (.RBRN):	3467878
Reactant (.RCT):	1-acetoxy-1-(4-benzyloxy-3-methoxy-phenyl)-2-nitro-propane
Product BRN (.PBRN):	3222448, 3483237
Product (.PRO):	(1RS:2RS)-2-acetylamino-1-(3-methoxy-4-benzyloxy-phenyl)-propanol-(1), N-hydroxy-N-<2-hydroxy-2-(4-benzyloxy-3-methoxy-phenyl)-1-methyl-ethyl>-acetamide
No. of React. Details (.NVAR):	1

Reaction Details:
RX

Reaction RID (.RID):	519302.1
Reaction Classification (.CL):	Preparation
Reagent (.RGT):	ethanol, acetic acid, aqueous hydrochloric acid
Temperature (.T):	50 - 60 Cel
Other Conditions (.COND):	weiteres Reagens: Blei-Kathoden; Behandlung der Reaktionsloesung mit Natriumacetat
Note(s) (.COM):	Handbook
Reference(s):	1. v. Fodor, Chem.Ber., CODEN: CHBEAM, 76, <1943>, 1216, 1217, 1219

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

=> => fil hcap
FILE 'HCAPLUS' ENTERED AT 14:43:44 ON 12 OCT 2005
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FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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=> fil zcap
FILE 'ZCAPLUS' ENTERED AT 14:43:47 ON 12 OCT 2005
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FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

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=> fil lreg
FILE 'LREGISTRY' ENTERED AT 14:43:50 ON 12 OCT 2005
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

=> fil reg
FILE 'REGISTRY' ENTERED AT 14:43:52 ON 12 OCT 2005
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6
DICTIONARY FILE UPDATES: 11 OCT 2005 HIGHEST RN 865062-68-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from  *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 14:43:54 ON 12 OCT 2005
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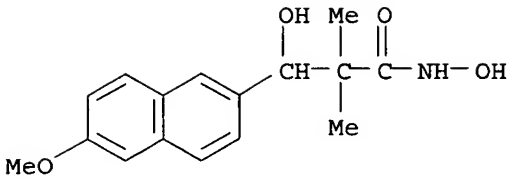
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  7, 2005 (20051007/UP).

=> d que l9
L1   (          1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2003-632197/APPS
L2                  SEL  PLU=ON  L1 1- RN :       98 TERMS
L3   (         98)SEA FILE=REGISTRY ABB=ON  PLU=ON  L2
L4   (         53)SEA FILE=REGISTRY ABB=ON  PLU=ON  NC5-C6/ES AND L3
L5   (          9)SEA FILE=REGISTRY ABB=ON  PLU=ON  C6-C6/ES AND L3
L6   (          6)SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L4
L7   (          4)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 AND (SI/ELS OR BR/ELS)
L8   (          2)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L7
L9               1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND N/ELS


=> d ide l9
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y


L9   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   656802-93-6  REGISTRY
ED   Entered STN:  02 Mar 2004
CN   2-Naphthalenepropanamide, N,β-dihydroxy-6-methoxy-α,α-
     dimethyl- (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C16 H19 N O4
SR   CA
LC   STN Files:  CA, CAPLUS, TOXCENTER, USPATFULL
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> => d his l11

(FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005)
L11 2 DUP REM L10 (1 DUPLICATE REMOVED)
SAVE TEMP L11 HOF197MULS2/A

FILE 'STNGUIDE' ENTERED AT 14:45:55 ON 12 OCT 2005

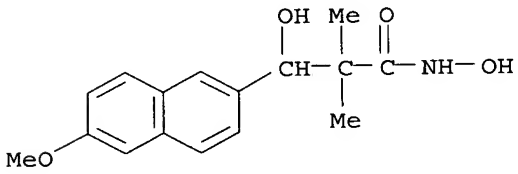
=> d que l11
L1 (1)SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-632197/APPS
L2 SEL PLU=ON L1 1- RN : 98 TERMS
L3 (98)SEA FILE=REGISTRY ABB=ON PLU=ON L2
L4 (53)SEA FILE=REGISTRY ABB=ON PLU=ON NC5-C6/ES AND L3
L5 (9)SEA FILE=REGISTRY ABB=ON PLU=ON C6-C6/ES AND L3
L6 (6)SEA FILE=REGISTRY ABB=ON PLU=ON L5 NOT L4
L7 (4)SEA FILE=REGISTRY ABB=ON PLU=ON L6 AND (SI/ELS OR BR/ELS)
L8 (2)SEA FILE=REGISTRY ABB=ON PLU=ON L6 NOT L7
L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON L8 AND N/ELS
L10 3 SEA L9
L11 2 DUP REM L10 (1 DUPLICATE REMOVED)

=> d ibib ed ab hitstr l11 1
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:120672 HCAPLUS
DOCUMENT NUMBER: 140:177322
TITLE: Hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases
INVENTOR(S): Maduskuie, Thomas P.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004012663 A2 20040212 WO 2003-US23989 20030731
WO 2004012663 A3 20040708
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004063698 A1 20040401 US 2003-632197 20030731
PRIORITY APPLN. INFO.: US 2002-400237P P 20020801
OTHER SOURCE(S): MARPAT 140:177322
ED Entered STN: 13 Feb 2004
AB MMP or TACE-inhibiting hydroxamic acid derivs. for use in treatment of diseases are disclosed. Thus, 3,N-dihydroxy-2,2-dimethyl-3-[6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I), 4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II), N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpropionamide (IV) as well as 23 other compds. were synthesized and tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's ≤ 10 μM.
IT **656802-93-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)
RN 656802-93-6 HCAPLUS
CN 2-Naphthalenepropanamide, N,β-dihydroxy-6-methoxy-α,α-dimethyl- (9CI) (CA INDEX NAME)



=> d ibib ab hitstr l11 2
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L11 ANSWER 2 OF 2 USPATFULL on STN
ACCESSION NUMBER: 2004:83242 USPATFULL
TITLE: Hydantoin derivatives as inhibitors of matrix metalloproteinases and/or TNF-alpha converting enzyme
INVENTOR(S): Maduskuie, Thomas P., Wilmington, DE, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004063698	A1	20040401	
APPLICATION INFO.:	US 2003-632197	A1	20030731	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-400237P	20020801 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000	
NUMBER OF CLAIMS:	18	
EXEMPLARY CLAIM:	1	
LINE COUNT:	3217	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compounds of Formula (I): ##STR1##

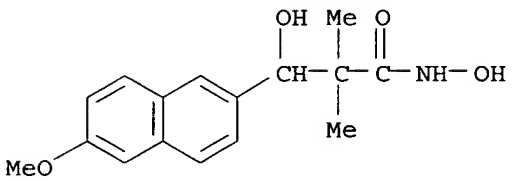
or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein the variables A, R.sup.1, R.sup.2, R.sup.3, R.sup.4, Z, U, X, Y, Z.sup.a, and n are defined are as defined herein, which are useful as inhibitors of matrix metalloproteinases (MMP) and/or TNF-α converting enzyme (TACE), or a combination thereof.

IT **656802-93-6P**

(hydroxamic acid derivative inhibitors of matrix metalloproteinases and/or TNFα converting enzyme for use in treatment of diseases)

RN 656802-93-6 USPATFULL

CN 2-Naphthalenepropanamide, N,β-dihydroxy-6-methoxy-α,α-dimethyl- (9CI) (CA INDEX NAME)



```
=> => fil hcap
FILE 'HCAPLUS' ENTERED AT 08:31:12 ON 13 OCT 2005
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FILE COVERS 1907 - 13 Oct 2005  VOL 143 ISS 16
FILE LAST UPDATED: 12 Oct 2005  (20051012/ED)

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=> fil medline'
'MEDLINE'' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'HCAPLUS'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> fil medline
FILE 'MEDLINE' ENTERED AT 08:31:18 ON 13 OCT 2005

 FILE LAST UPDATED: 12 OCT 2005 (20051012/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available.  For details enter HELP
 RLOAD at an arrow promt (=>).  See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> fil wpix
FILE 'WPIX' ENTERED AT 08:31:28 ON 13 OCT 2005
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FILE LAST UPDATED:          11 OCT 2005       <20051011/UP>
```

```
MOST RECENT DERWENT UPDATE:     200565        <200565/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
    PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
    FOR DETAILS. <<<

=> fil embase
FILE 'EMBASE' ENTERED AT 08:31:32 ON 13 OCT 2005
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 FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> file biosis
FILE 'BIOSIS' ENTERED AT 08:31:35 ON 13 OCT 2005
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 October 2005 (20051012/ED)

FILE RELOADED: 19 October 2003.

=> fil pascal
FILE 'PASCAL' ENTERED AT 08:31:39 ON 13 OCT 2005
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FILE LAST UPDATED: 10 OCT 2005       <20051010/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
    IN THE BASIC INDEX (/BI) FIELD  <<<
```

```
=> fil jicst
FILE 'JICST-EPLUS' ENTERED AT 08:31:42 ON 13 OCT 2005
COPYRIGHT (C) 2005 Japan Science and Technology Agency (JST)

FILE COVERS 1985 TO 12 OCT 2005 (20051012/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED
TERM (/CT) THESAURUS RELOAD.

=> fil caba
FILE 'CABA' ENTERED AT 08:31:45 ON 13 OCT 2005
COPYRIGHT (C) 2005 CAB INTERNATIONAL (CABI)

FILE COVERS 1973 TO 7 Oct 2005 (20051007/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The CABA file was reloaded 7 December 2003.  Enter HELP RLOAD for details.

=> fil cancerlit
FILE 'CANCERLIT' ENTERED AT 08:31:49 ON 13 OCT 2005

 FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

 On July 28, 2002, CANCERLIT was reloaded.  See HELP RLOAD for details.

 CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary.  Enter HELP THESAURUS for details.

 This file contains CAS Registry Numbers for easy and accurate substance
 identification.

=> fil drugu
FILE 'DRUGU' ENTERED AT 08:31:53 ON 13 OCT 2005
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FILE LAST UPDATED: 11 OCT 2005        <20051011/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


=> fil scisearch
FILE 'SCISEARCH' ENTERED AT 08:31:58 ON 13 OCT 2005
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FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

=> fil conf
FILE 'CONF' ENTERED AT 08:32:00 ON 13 OCT 2005
COPYRIGHT (c) 2005 FIZ Karlsruhe

FILE LAST UPDATED: 7 OCT 2005        <20051007/UP>
FILE COVERS 1976 TO DATE.
```

=> fil confsci
FILE 'CONFSCI' ENTERED AT 08:32:09 ON 13 OCT 2005

FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

=> fil dissabs
FILE 'DISSABS' ENTERED AT 08:32:14 ON 13 OCT 2005

FILE COVERS 1861 TO 29 SEP 2005 (20050929/ED)

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 08:32:16 ON 13 OCT 2005

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

```
=> d que l20
L11 (          1) SEA FILE=WPIX ABB=ON  PLU=ON  (RADLBS/DCN OR RADLCX/DCN OR
                  RADLCZ/DCN OR RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR
                  RADL2W/DCN OR RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR
                  RADL3C/DCN OR RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR
                  RADL3W/DCN OR RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR
                  RADL4D/DCN OR RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR
                  RADL42/DCN OR RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR
                  0125-21301/DCN OR 0125-21302/DCN OR 0125-21303/DCN OR 0125-2130
                  4/DCN OR 0125-21305/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR
                  0125-21308/DCN OR 0125-21309/DCN OR 0125-21310/DCN OR 0125-2131
                  1/DCN OR 0125-21312/DCN OR 0125-21313/DCN OR 0125-21314/DCN)
L12 (      27282) SEA FILE=WPIX ABB=ON  PLU=ON  ((D621 OR D622)(P) (G011 OR G012
                  OR G013 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1
                  ,M2,M3,M4,M5,M6
L13 (        328) SEA FILE=WPIX ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX
                  ) (L) (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR
                  (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR
                  ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A)(?
                  CONVERT?/BIX OR ?CONVERS?/BIX)))
L14 (         40) SEA FILE=WPIX ABB=ON  PLU=ON  (L11 OR L12) AND L13
L15 (       3929) SEA FILE=WPIX ABB=ON  PLU=ON  (MMP/BIX OR (?MATRIX?/BIX(2A)(?ME
                  TALLOPROT?/BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR
                  ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR
                  (?ALPHA?/BIX(2A)(?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A)
                  (?INHIBIT?/BIX OR ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/B
                  IX OR ?INTERRUPT?/BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR
                  ?PREVENT?/BIX OR ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX
                  OR ?BLOCK?/BIX OR STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)
L16 (        304) SEA FILE=WPIX ABB=ON  PLU=ON  L15 (L) (?HYDANTOI?/BIX OR
                  ?HYDROXAM?/BIX)
L17           38  SEA FILE=WPIX ABB=ON  PLU=ON  L14 AND L16
L19          196  SEA FILE=WPIX ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX
                  ) (L) (?QUINOLIN?/BIX)
L20           14  SEA FILE=WPIX ABB=ON  PLU=ON  L17 AND L19


=> d que l31
L1                QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L6                QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7                QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                  R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                  R ?PYRIMIDIN? OR ?BENZENE?
L21               QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                  R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                  2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                  ?))
L23          15230  SEA FILE=MEDLINE ABB=ON  PLU=ON  HYDANTOINS+PFT,NT/CT
L24            485  SEA FILE=MEDLINE ABB=ON  PLU=ON  L23 (L) AA
L25              3  SEA FILE=MEDLINE ABB=ON  PLU=ON  L24 AND L21
L26            367  SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (L) L21
L27            970  SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (10A) (L6 OR L7)
L28             34  SEA FILE=MEDLINE ABB=ON  PLU=ON  L26 AND L27
L29             14  SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (7A) L6
L30              4  SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L29
L31              7  SEA FILE=MEDLINE ABB=ON  PLU=ON  L25 OR L30


=> d que l39
L1                QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
```

```
L6              QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7              QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                R ?PYRIMIDIN? OR ?BENZENE?
L21             QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                ?))
L32         50409 SEA FILE=EMBASE ABB=ON  PLU=ON  "HYDANTOIN DERIVATIVE"+PFT,NT/C
                T
L33           187 SEA FILE=EMBASE ABB=ON  PLU=ON  L32 AND L21
L36           391 SEA FILE=EMBASE ABB=ON  PLU=ON  L1 (L) L21
L37            17 SEA FILE=EMBASE ABB=ON  PLU=ON  L33 AND L36
L38            11 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 AND (L6 OR L7)
L39            17 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 OR L38


=> d his l47

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'
     ENTERED AT 08:16:50 ON 13 OCT 2005)
L47            53 DUP REM L46 (21 DUPLICATES REMOVED)

=> d que l47
L1              QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L6              QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7              QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                R ?PYRIMIDIN? OR ?BENZENE?
L21             QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                ?))
L40          6407 SEA L1 (7A) (L6 OR L7)
L41         20700 SEA L1/TI,IT,CC,CT,ST,STP
L42          4900 SEA L40 AND L41
L43          1538 SEA L1 (L) L21
L44            87 SEA L42 AND L43
L45        269429 SEA L21/TI,IT,CC,CT,ST,STP
L46            74 SEA L44 AND L45
L47            53 DUP REM L46 (21 DUPLICATES REMOVED)


=> dup rem l20 l31 l39 l47
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FILE 'SCISEARCH' ENTERED AT 08:33:16 ON 13 OCT 2005
Copyright (c) 2005 The Thomson Corporation
PROCESSING COMPLETED FOR L20
PROCESSING COMPLETED FOR L31
PROCESSING COMPLETED FOR L39
PROCESSING COMPLETED FOR L47
L51            85 DUP REM L20 L31 L39 L47 (6 DUPLICATES REMOVED)
                  ANSWERS '1-14' FROM FILE WPIX
                  ANSWERS '15-21' FROM FILE MEDLINE
                  ANSWERS '22-37' FROM FILE EMBASE
                  ANSWERS '38-53' FROM FILE BIOSIS
                  ANSWERS '54-75' FROM FILE PASCAL
                  ANSWER '76' FROM FILE CANCERLIT
                  ANSWERS '77-78' FROM FILE DRUGU
                  ANSWERS '79-85' FROM FILE SCISEARCH

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 08:33:24 ON 13 OCT 2005
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  7, 2005 (20051007/UP).
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=> d iall abeq tech abex
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L51 ANSWER 1 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-630225 [64] WPIX
DOC. NO. CPI: C2005-189027
TITLE: New substituted **hydroxamic** acid derivatives are **matrix metalloproteinase inhibitors** and **tumor necrosis** factor **inhibitors** useful for treating e.g. inflammatory, infectious, immunological and malignant diseases.
DERWENT CLASS: B03
INVENTOR(S): JAIN, M R; LOHRAY, B B; LOHRAY, V B; THOMBARE, P S
PATENT ASSIGNEE(S): (CADI-N) CADILA HEALTHCARE LTD
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2005077937	A1	20050825	(200564)*	EN	43	C07D401-12

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005077937	A1	WO 2005-IN10	20050107

PRIORITY APPLN. INFO: IN 2004-MU22 20040109
INT. PATENT CLASSIF.:
MAIN: C07D401-12
SECONDARY: A61K031-4025; A61K031-4709; A61P029-00; C07D405-14; C07D409-14
BASIC ABSTRACT:
WO2005077937 A UPAB: 20051006
NOVELTY - Substituted **hydroxamic** acid derivatives, or their salts, solvates, stereoisomers or tautomers are new.
DETAILED DESCRIPTION - Substituted **hydroxamic** acid derivatives of formula (I), or their salts, solvates, stereoisomers or tautomers are new.
A = COR1, COOH, CH2COOH, CONHOH, CONHOR1, N(OH)COR1, C(=NOR1)NHR1, SH, CH2SH, SO2NHR1 or S(=NH)2R1;
R1 = linear or branched 1-8C alkyl, 3-7C cycloalkyl, acyl, aryl, aralkyl, alkylamino carbonyl, (hetero)arylamino carbonyl, (hetero)aralkylamino carbonyl or heterocyclyl aminocarbonyl (all optionally substituted by T) or H;
R2 and R3 = linear or branched 1-8C alkyl, 3-7C cycloalkyl, acyl, 3-7C cycloalkyl, aryl, aralkyl, aralkyl, heteroaryl, heterocycle (all

optionally substituted by T), H, or halo;
X = T1;
T1 = 3-13C carbocyclic residue (optionally substituted by T) or 5 - 14-membered heterocyclic group containing 1 - 4 heteroatoms selected from N, O and S;
Z = 3-13C carbocyclic residue (substituted by alkenyl, alkynyl, alkoxy alkyl (all optionally substituted), (CH2)r-(3-6C)cycloalkyl, (CH2)r-cycloalkenyl, (CH2)r-phenyl, or (CH2)r-3 - 14-membered heterocycle comprising 1 - 4 heteroatoms selected from N, O and S) or 5 - 14-membered heterocyclic system containing 1 - 4 N, O or S;
n = 1 - 2;
r = 0 - 6;
Y = (CR'Rx)p, O(CR'Rx)p, (CR'Rx)pO, C(O)(CR'Rx)p, (CR'Rx)C(O), NR'(CR'Rx)p, NR'NRx, (CR'Rx)pNR', NR'C(O)(CR'Rx)p, CONR'(CR'Rx)p, (CR'Rx)pNR'C(O), (CR'Rx)pNR'C(O), (CR'R')pC(O)NR', NR'CONR', (CR'Rx)pS(O)q, or S(O)q(CR'Rx)p;
R4 = H, SR', halogen, NR'Rx, OR', CN, NO2, 1-10C alkyl-Ra, 2-10C alkenyl-Ra, 2-10C alkynyl-Ra, (CR'Rx)p-Ra, O(CR'Rx)pRa, (CR'Rx)pO(CR'Rx)pRa, (CR'Rx)pNR'(CR'Rx)pRa, (CR'Rx)pC(O)(CR'Rx)pRa, (CR'Rx)pOC(O)(CR'Rx)pRa, (CR'Rx)pC(O)O(CR'Ra)pRa, (CR'Rx)pNR'C(O)(CR'Rx)pRa, (CR'Rx)pC(O)NR'(CR'Rx)pRa, (CR'Rx)pS(O)q(CR'Rx)pRa, (CR'Rx)pS(O)qNR'C(CR'Rx)pRa, (CR'Rx)pNR'S(O)q(CR'Rx)pRa, (CR'Rx)pOC(O)NR'(CR'Rx)pRa, or (CR'Rx)pNR'C(O)O(CR'Rx)pRa;
p and q = 0 - 2;
R' and Rx = T2;
T2 = linear or branched 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl (all optionally substituted), H or alkyl;
Ra = halogen or T2;and
T = a substituent.
An INDEPENDENT CLAIM is included for preparation of (I).
ACTIVITY - Antiinflammatory; Antimicrobial; Antiarthritic; Antirheumatic; Antiulcer; Vulnerary; Osteopathic; Gastrointestinal-Gen.; Cytostatic; Respiratory-Gen.; Antimalarial; Antiasthmatic; Neuroprotective; Nootropic; Immunosuppressive; Immunomodulator; Antiallergic; Antibacterial; Vasotropic; Dermatological; Antiarteriosclerotic; Cardiant; Cerebroprotective; Vulnerary; Anticonvulsant; Antiparkinsonian; Antimigraine; Antidepressant; Analgesic; Anti-HIV; Ophthalmological.
MECHANISM OF ACTION - **Matrix** degrading **metalloproteinase** (**MMP**) **inhibitor**; **Tumor necrosis** factor- alpha (**TNF**- alpha) **inhibitor**; **Tumor necrosis** factor- **alpha converting** enzyme (**TACE**) **inhibitor**; Aggrecanase **inhibitor.** 2-(3-Amino-3-(4-(2-isopropoxymethyl-**quinolin**-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid hydroxyamide (a) was tested for **TNF** - alpha **inhibitory** activity using rat whole blood assay. Rats were anaesthetized and blood (6 - 8 ml) was collected in a tube containing heparin (100 IU/ml). Blood sample (500 mu l) was incubated with (a) (10 mu M) for 15 minutes at 37 deg. C. LPS (1 mu g/ml) was added and the mixture was further incubated for 5 hours at 37 deg. C. The reaction was terminated by placing the sample over ice for 15 minutes at 4 deg. C. The plasma was collected and **TNF**- alpha level was estimated by ELISA method. The % inhibition at 10 mu M dose of (a) was 94%.
USE - In the preparation of pharmaceutical composition and in the manufacture of medicament for treatment or prophylaxis of inflammatory, infectious, immunological and malignant diseases in a mammal e.g. human; for treating diseases associated with excess of **tumor necrosis** factor- alpha production or secretion (claimed) such as

arthritis (e.g. osteoarthritis, rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration); abnormal wound healing; periodontal disease; bone disease (e.g. osteoporosis, Paget's disease), tumor metastasis, inflammatory bowel disease, Crohn's disease, emphysema, malaria, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reaction, allergic contact hypersensitivity, cancer (such as solid tumor including colon cancer, breast cancer, lung cancer and prostrate cancer and hematopoietic malignancies including leukemia and lymphomas), mycobacterial infection, meningitis, graft rejection, restenosis, epidermolysis bullosa, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, hyperoxic alveolar injury, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, corneal scarring, scleritis, AIDS, sepsis and septic shock.

ADVANTAGE - The compounds are potent **matrix metalloproteinase** (**MMP**), aggrecanase and **tumor necrosis** factor **inhibitors.** The compound exhibits enhanced activities without toxic effects or with reduced toxic effects.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B14-A01; B14-A02; B14-A03B; B14-C01; B14-C03; B14-C09; B14-D03; B14-E08; B14-E10C1; B14-E11B; B14-F01B; B14-F01G; B14-F02C; B14-F02D1; B14-F07; B14-G01B; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-H01B; B14-J01A1; B14-J01A3; B14-J01A4; B14-K01; B14-K01F; B14-N01; B14-N03; B14-N06B; B14-N16; B14-N17B; B14-S04; B14-S06

TECH UPTX: 20051006

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) involves:
(1) process A: converting a disubstituted pyrrolidine-2-one derivative of formula (II) to a corresponding ester of formula (III); and converting (III) to hydroxamide derivative of formula (I) (where A is CONHOH, X-Y-Z is phenyl (substituted by OCH2Z on 4-position));
(2) process B: optionally converting (III) to 3-substituted amine derivative of formula (IV); and converting (IV) to hydroxamide derivative of formula (I) (where A is CONHOH, R4 is NH2, X-Y-Z is phenyl (substituted on 4-position by OCH2-Z));
(3) process C: optionally converting (III) to hydroxamic acid of formula (I) (where A is COOH, X-Y-Z is phenyl (substituted on 4-position by OCH2-Z)); and
(4) process D: optionally converting (IV) to hydroxamic acid of formula (I) (where A is COOH, R4 is NH2, X-Y-Z is phenyl (substituted on 4-position by OCH2Z)).

ABEX UPTX: 20051006

SPECIFIC COMPOUNDS - 37 Compounds are specifically claimed as (I) e.g. 2-(3-amino-3-(4-(2-isopropoxymethyl-**quinolin**-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid hydroxyamide.

ADMINISTRATION - (I) Is administered in the form of tablets, pills, capsules, powder, granules, syrup, solution or suspension (claimed) orally. No dosage given.

EXAMPLE - To a solution of 2-(3-tert-butoxycarbonylamino-3-(4-hydroxy-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (2.0 g), (2-methoxymethyl-**quinoline**-4-yl)-methanol(1.06 g) and triphenylphosphine (1.37 g) in dichloromethane (20 ml) at 0degreesC was added diisopropyl azodicarboxylate (DIAD) (1.44 g). The mixture was stirred at 25 - 30degreesC for 24 hours and then quenched with water (20 ml) and worked up to give 2-(3-tert-butoxycarbonylamino-3-(4-(2-methoxymethyl-**quinoline**-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (1.8 g) (A). To a solution of (A) (1.8 g) in dichloromethane (10 ml) at 0degreesC was added trifluoroacetic acid (3.38 g) dropwise. The mixture was stirred at 25 - 30degreesC for 4 hours. Water (10 ml) was added to the mixture, the pH of the mixture was adjusted to 10 by adding 10% aqueous sodium bicarbonate solution and worked up to give 2-(3-amino-3-(4-(2-methoxymethyl-**quinolin**-4-ylmethoxy)phenyl)-2-oxo-pyrrolidin-1-yl)-4-methyl-pentanoic acid methyl ester (1.4 g) (B). To a hot solution of hydroxylamine hydrochloride (3.83 g) in methanol (30 ml) was added a solution of sodium hydroxide (3.31 g) in methanol (30 ml). The mixture was kept under stirring at 25 - 30degreesC for 30 minutes and then cooled to 5 - 10degreesC, filtered and freshly prepared solution of the hydroxylamine was added to (B) (1.4 g) in methanol (10 ml) at 5 - 10degreesC. The mixture was stirred at 25 - 30degreesC for 2 hours, acidified to pH 6.0 - 6.5 with 1N hydrochloride. The **hydroxamic** acid was precipitated out to give 2-(3-amino-3(4-(2-methoxymethyl-**quinolin**-4-ylmethoxy)-phenyl)-2-oxo-pyrrolidin-1-yl)-4-methy-1-pentanoic acid hydroxyamide (1.0 g, 69.5% yield).

DEFINITIONS - Preferred Definitions:
Z=**quinolinyl**, pyrimidinyl or quinazolinyl; and
T=OH, oxo, halogen, thio, nitro, amino, cyano, formyl, alkyl, haloalkyl, per-haloalkyl, alkoxy, haloalkoxy, per-haloalkoxy, alkenyl, alkynyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryloxy, heterocyclyl, (hetero)aryl, (hetero)cycloalkyl, (hetero)aralkyl, heteroaryloxy, (hetero)aralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, mono or di-substituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfonyloxy, alkylsulfonyloxy, alkoxycoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid or its derivative.

=> d iall abeq tech abex 2-14
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L51 ANSWER 2 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-594142 [57] WPIX
DOC. NO. CPI: C2004-216155
TITLE: New sulfonyl hydroxamic acid derivatives are soluble human cluster differentiation-23 inhibitors useful to treat or prevent e.g. autoimmune, allergic and inflammatory diseases.
DERWENT CLASS: B05
INVENTOR(S): BRUTON, G

PATENT ASSIGNEE(S): (GLAX) GLAXO GROUP LTD
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004067502	A1	20040812	(200457)*	EN	29	C07C317-44

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004067502	A1	WO 2004-EP954	20040130

PRIORITY APPLN. INFO: GB 2003-2431 20030130
INT. PATENT CLASSIF.:
MAIN: C07C317-44
SECONDARY: A61K031-4375; A61P037-00; C07D215-12
BASIC ABSTRACT:
WO2004067502 A UPAB: 20040907
NOVELTY - Sulfonyl **hydroxamic** acid derivatives (I) or their isomers are new.
DETAILED DESCRIPTION - Sulfonyl **hydroxamic** acid derivatives of formula (I) or their isomers are new.
R = H, alkyl, alkoxy, alkenyl, alkynyl, (hetero)aryl or heterocyclyl; and
R1 = (hetero)bicyclyl.
INDEPENDENT CLAIMS are also included for
(1) a thioamine derivative of formula (II);
(2) a thiohydroxylamine derivative of formula (III);
(3) acid derivative of formula (VIII); and
(4) preparation of (I).
P = protecting group.
ACTIVITY - Immunosuppressive; Antiallergic; Antiinflammatory; Antiasthmatic; Ophthalmological; Dermatological.
MECHANISM OF ACTION - Soluble human cluster differentiation-23 (S-CD23) **inhibitor**; **Matrix metalloprotease inhibitor**; Collagenase **inhibitor**.
The ability of (I) to inhibit S-CD23 was assessed using plasma membranes from RPMI 8866 cells, human Epstein-Barr virus transformed B-cell lines expressing high levels of CD23. The results showed that median inhibitor concentration (IC50) value of N-hydroxy-2-phenyl-3-(3-**quinolin**-3-ylmethanesulfonyl)-propionamide was 0.01 micro M.
USE - (I) is useful in the treatment or prevention of disorders in which the overproduction of s-CD23 is implicated (claimed) such as autoimmune diseases, allergic diseases (asthma, rhinitis, allergic conjunctivitis, eczema, atopic dermatitis and anaphylaxis) and inflammatory diseases.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D02; B10-A09A; B14-D07C; B14-G02; B14-G02A;

B14-K01; B14-K01A; B14-N03; B14-N17

TECH UPTX: 20040907

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises either:
(1) deprotection of (II);
(2) oxidation of (III);
(3) conversion of (I) to another compound of (I); and
(4) reaction of (VIII) with a hydroxylamine or its salt.

ABEX UPTX: 20040907

SPECIFIC COMPOUNDS - 2 compounds (I) are specifically claimed e.g. N-hydroxy-2-phenyl-3-(3-quinolin-3-ylmethanesulfonyl)-propionamide (Ia).

ADMINISTRATION - Administration of (I) is 1 mg-1 g, orally, parenterally, sublingually, transdermally or by inhalation.

EXAMPLE - A suspension of 2-phenyl-3-(3-quinolylmethanesulfonyl)-propionoic acid hydrochloride (30 mg) in dichloromethane (5 ml) was treated with oxalyl chloride (0.5 ml) and dimethyl formamide (1 drop). After 1 hour the mixture was evaporated and the resulting solid suspended in dichloromethane (5 ml) and O-trimethylsilylhydroxylamine (0.5 ml) added. The reaction mixture was worked up to give N-hydroxy-2-phenyl-3-(3-quinolin-3-ylmethanesulfonyl)-propionamide (Ia) .

DEFINITIONS - Preferred Definitions:
R = aryl or alkoxy (preferably phenyl or propyloxy); and
R1 = heterobicyclyl (preferably quinoline).

L51 ANSWER 3 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-295066 [27] WPIX
CROSS REFERENCE: 2004-283028 [26]
DOC. NO. CPI: C2004-112879
TITLE: New **hydantoin** derivatives, useful for treatment of e.g. inflammatory diseases, autoimmune diseases and allergic/atopic diseases, are **tumor necrosis** factor **alpha converting** enzyme **inhibitors.**
DERWENT CLASS: B02 B03
INVENTOR(S): BURROWS, J N; TUCKER, H
PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
COUNTRY COUNT: 106
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004024721	A1	20040325	(200427)*	EN	67	C07D401-14
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
AU 2003263347	A1	20040430	(200462)			C07D401-14
NO 2005001788	A	20050613	(200545)			C07D401-14
EP 1551826	A1	20050713	(200546)	EN		C07D401-14
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR						
BR 2003014275	A	20050809	(200554)			C07D401-14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004024721	A1	WO 2003-GB3914	20030909
AU 2003263347	A1	AU 2003-263347	20030909
NO 2005001788	A	WO 2003-GB3914	20030909
		NO 2005-1788	20050412
EP 1551826	A1	EP 2003-795075	20030909
		WO 2003-GB3914	20030909
BR 2003014275	A	BR 2003-14275	20030909
		WO 2003-GB3914	20030909

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003263347	A1 Based on	WO 2004024721
EP 1551826	A1 Based on	WO 2004024721
BR 2003014275	A Based on	WO 2004024721

PRIORITY APPLN. INFO: GB 2002-21246 20020913
INT. PATENT CLASSIF.:
MAIN: C07D401-14
SECONDARY: A61K031-4166; A61K031-47; A61P043-00; C07D403-06
BASIC ABSTRACT:
WO2004024721 A UPAB: 20050823
NOVELTY - **Hydantoin** derivatives (I) are new.
DETAILED DESCRIPTION - **Hydantoin** derivatives of formula (I) and their salts are new.
Y1, Y2 = O;
Z1 = NR8, O or S;
n, t = 0 or 1;
W1 = CR1R2 or a bond;
V1 = a group of formula (a);
B1 = 2-4C alkenyl, 2-4C alkynyl, 5-6C cycloalkenyl (all optionally substituted by halo or R9), (hetero)aryl, heterocyclyl (optionally substituted by NO2, CF3, OCF3, halo, CN, 1-4C alkyl (optionally substituted by R9 or 1-4C alkoxy or one or more halo), 3-6C cycloalkyl (optionally substituted by R9 or one or more halo), (hetero)aryl (optionally substituted by halo or 1-4C alkyl), heterocyclyl (optionally substituted by 1-4C alkyl), S(O)mR11, SO2NR9R10, NR9SO2R11, NHCONR9R10, OR9, NR9R10, CONR9R10 and/or NR9COR10); or
B1 = 2-4C alkenyl or 2-4C alkynyl (optionally substituted by 1-4C alkyl, 3-6C cycloalkyl, (hetero)aryl, heterocyclyl (optionally substituted by one or more halo, nitro, CN, CF3, OCF3, CONHR9, CONR9R10, SO2R11, SO2NR9R10, NR9SO2R11, 1-4C alkyl or 1-4C alkoxy));
m = 0-2;
R1, R2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl or 5-6C cycloalkenyl (all optionally substituted by halo, CN, OH or 1-4C alkoxy) or H;
R3-R6 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, (hetero)aryl, heterocyclyl (optionally substituted by halo, nitro, CN, CF3, OCF3, 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 3-6C cycloalkyl (optionally substituted by one or more R17), (hetero)aryl (optionally substituted by one or more R17), heterocyclyl, OR18, S(O)mR19, COR19, CO2R18, CONR18R20, NR16COR18, SO2NR18R20 and/or NR16SO2R16) or H; or
CR1R3, CR3R4, CR3R5, CR5R6 = saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms NH, O, S, SO or SO2, where the ring is optionally substituted on C by 1-4C alkyl, F or 1-3C alkoxy and/or N by 1-4C alkyl, CO(1-3C alkyl) or SO2(1-3C alkyl);

R7 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, heteroalkyl, 3-7C cycloalkyl, (hetero)aryl or heterocyclyl (optionally substituted by halo, 1-4C alkyl, 1-4C alkoxy, 3-7C cycloalkyl, heterocyclyl, (hetero)aryl or heteroalkyl)) (all optionally substituted by halo, CN, 1-4C alkyl, nitro, halo(1-4C alkyl), heteroalkyl, (hetero)aryl, hydroxy(1-4C alkyl), 3-7C cycloalkyl, heterocyclyl, 1-4C alkoxy(1-4C alkyl), halo(1-4C alkoxy)(1-4C alkyl), CO(1-4C alkyl), OR12, CO2R21, S(O)mR25, NR21COR21, CONR21R22 and/or NHCOR21R22); or

CR3R7, (CR5R6)n = saturated 5-7 membered ring optionally containing a hetero atom of NH, O, S, SO or SO2, where the ring is optionally substituted on C by 1-4C alkyl, F or 1-3C alkoxy and/or N by 1-4C alkyl, CO(1-3C alkyl) or SO2(1-3C alkyl);

R8 = H or CH3;

R9, R10, R12, R13 = H, 1-6C alkyl or 3-6C cycloalkyl; or

NR9R10 = heterocyclic 4-7 membered ring;

R11 = 1-6C alkyl or 3-6C cycloalkyl;

R14 = H, CN, NR23R24 or 1-4C alkyl (optionally substituted by halo, OR23 or NR23R24);

R16, R23, R24 = H or 1-6C alkyl;

R17 = halo, 1-6C alkyl, 3-6C cycloalkyl or 1-6C alkoxy;

R19, R25 = 1-6C alkyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, saturated heterocyclyl, (hetero)aryl, aryl(1-4C alkyl) or heteroaryl(1-4C alkyl) (all optionally substituted by one or more halo);

R18 = 1-6C alkyl, 3-6C cycloalkyl, 5-6C cycloalkenyl, saturated heterocyclyl, (hetero)aryl, aryl(1-4C alkyl), heteroaryl(1-4C alkyl) (optionally substituted by one or more halo) or H;

R20 = H, 1-6C alkyl or 3-6C cycloalkyl; or

NR18R20 = heterocyclic 4-7 membered ring; and

R21, R22 = H, 1-4C alkyl, halo(1-4C alkyl), aryl or aryl(1-4C alkyl).

ACTIVITY - Antiinflammatory; Immunosuppressive; Antiallergic; Cardiovascular-Gen.; Vasotropic; Cytostatic; Respiratory-Gen.; Antiasthmatic; Antiarthritic; Antirheumatic; Antipsoriatic; Dermatological.

MECHANISM OF ACTION - Metalloproteinase **inhibitor**; **Tumor Necrosis** Factor- **alpha** **converting** enzyme (**TACE**) **inhibitor.**

(I) were assessed for TACE inhibitory activity using partially purified enzyme assay. The results showed that MIC value of 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione was 130 nM.

USE - (I) are useful in the manufacture of medicament for the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man (claimed), respiratory disorders such as asthma or chronic obstructive pulmonary disease, rheumatoid arthritis, Crohn's disease and psoriasis.

ADVANTAGE - (I) have good potency and/or pharmacokinetic properties.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B14-C03; B14-C09B; B14-D07C; B14-E10C; B14-F01; B14-F02; B14-F05; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-K01; B14-K01A; B14-N17C

TECH UPTX: 20040426

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Claimed preparation of (I) comprises conversion of a ketone or aldehyde of formula (II) into (I), if necessary

(a) converting (I) into another compound of formula (I);

(b) removing any protecting groups; and

(c) forming a pharmaceutically acceptable salt or in vivo hydrolyzable ester.

ABEX UPTX: 20040426

SPECIFIC COMPOUNDS - 14 compounds (I) are specifically disclosed e.g. 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione of formula (Ia).

ADMINISTRATION - Administration of (I) is 0.5-0.75 (preferably 0.5-30) mg/kg/day, orally, parenterally, topically, rectally or by inhalation. EXAMPLE - 1-(2-Hydroxy-2-phenylethyl)-3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)pyrrolidin-2-one (120 mg) was dissolved in dichloromethane (4 ml). 4-Methylmorpholine N-oxide (53 mg) and 4A molecular sieves (300 mg) were added. The reaction was stirred for 10 minutes before addition of tetra-n-propylammonium per-ruthenate (VII) (6 mg). The reaction was stirred for 30 minutes and poured onto a silica bond elute (5 g) and eluted with ethylacetate to give 3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (90 mg). To a stirred solution of the above product in ethanol (2 ml) and water (2 ml) was added ammonium carbonate (110 mg) and potassium cyanide (25 mg). The mixture was worked up to give 5-(3-methyl-3-(4-(2-methylquinolin-4-ylmethoxy)phenyl)-2-oxopyrrolidin-1-ylmethyl)-5-phenylimidazolidine-2,4-dione (5 mg).

DEFINITIONS - Preferred Definitions:
B1 = (hetero)aryl or heterocyclyl (all optionally substituted by nitro, CF3, OCF3, halo, 1-4C alkyl (optionally substituted by one or more halo), 2-4C alkynyl, heteroaryl, OR9, CN, NR9R10, CONR9R10 and/or NR9COR10 (preferably phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thienopyridyl, 1,6-naphthyridinyl, 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 1,6-naphthyridinyl, thienopyrimidinyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indolizinyl, isobenzofuranyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl or isoindolinyl (each optionally substituted by nitro, CF3, OCF3, halo, 1-4C alkyl (optionally substituted by one or more fluoro), 2-4C alkynyl, heteroaryl, OR9, CN, NR9R10, CONR9R10 and/or NR9COR10 or 2-methylquinolin-4-yl or 2,5-dimethylphenyl); or
B1 = 2-4C alkenyl or 2-4C alkynyl optionally substituted by 1-4C alkyl, 3-6C cycloalkyl or heterocyclyl (preferably vinyl or ethynyl optionally substituted by 1-4C alkyl);
t = 1;
R7 = H, 1-4C alkyl, halo(1-4C alkyl), hydroxy(1-4C alkyl), 1-4C alkoxy(1-4C alkyl) or aryl; and
R14 = H, CH3 or NH2.

L51 ANSWER 4 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-328245 [30] WPIX
DOC. NO. CPI: C2004-124409
TITLE: New hydantoin derivatives useful in the treatment of e.g. HIV infection, psoriasis, autoimmune diseases, tumor, gingivitis, and stroke.
DERWENT CLASS: B02 B03
INVENTOR(S): SHEPPECK, J
PATENT ASSIGNEE(S): (SHEP-I) SHEPPECK J; (BRIM) BRISTOL-MYERS SQUIBB CO
COUNTRY COUNT: 107
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

US 2004067996 A1 20040408 (200430)* 43 A61K031-4166
WO 2004033632 A2 20040422 (200430) EN C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
VC VN YU ZA ZM ZW
AU 2003282920 A1 20040504 (200465) A61K031-4166
EP 1546109 A2 20050629 (200543) EN C07D215-20
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
MC MK NL PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004067996	A1 Provisional	US 2002-416349P	20021004
		US 2003-677988	20031002
WO 2004033632	A2	WO 2003-US31347	20031002
AU 2003282920	A1	AU 2003-282920	20031002
EP 1546109	A2	EP 2003-774537	20031002
		WO 2003-US31347	20031002

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003282920	A1 Based on	WO 2004033632
EP 1546109	A2 Based on	WO 2004033632

PRIORITY APPLN. INFO: US 2002-416349P 20021004; US
2003-677988 20031002

INT. PATENT CLASSIF.:
MAIN: A61K031-4166; C07D215-20; C12N000-00
SECONDARY: A61K031-4439; A61K031-4709; C07D233-72; C07D401-12

BASIC ABSTRACT:
US2004067996 A UPAB: 20040511
NOVELTY - **Hydantoin** derivatives (I), their salts and prodrugs are new.
DETAILED DESCRIPTION - **Hydantoin** derivatives of formula (I), their salts and prodrugs are new.
E1 = CRaRa1;
R1 = e.g. Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkenylene-Q or (E1)tO(E1)s-Q;
L = e.g. bond or CO;
Q = e.g. 3-13C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, S, or S(O)p) (both optionally substituted), H, or CF3;
Z'a = 5 - 6-membered (hetero)aryl (optionally containing 1 - 3 heteroatoms) or (hetero)aryl (optionally fused to 5 - 6 membered carbocycle or heterocycle optionally containing 1 - 2 heteroatoms, and 1 - 2 double bonds) (both optionally substituted);
R11 = W'-U'-X-Y'-Z-Ua-Xa-Ya-Za;
W' = (E1)m, 2-3C alkenylene or 2-3C alkynylene;
U' = e.g. O, C(O), C(O)O, OC(O), or S(O)p;
X = absent, 1-3C alkylene, 2-3C alkenylene or 2-3C alkynylene;
Y', Ya = absent, O, S(O)p or C(O);
Z = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted);

Ua = e.g. absent, O, C(O), C(O)O, OC(O), S(O)p, or NRa1S(O)2NRa1;
Xa = e.g. absent, 1-10C alkylene, or 2-10C alkynylene;
Za = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted);
Ra1 = e.g. 2-6C alkenyl, 1-6C alkyl, or 2-6C alkynyl (all optionally monosubstituted), or H;
R4, R5 = H, 1-4C alkyl, 2-4C alkenyl, or 2-4C alkynyl;
m = 0 - 3;
p = 0 - 2;
r, s = 0 - 4; and
t = 1 - 4.

Full Definitions are given in the DEFINITIONS (Full Definitions) section.

INDEPENDENT CLAIMS are included for the following:

(a) treatment of inflammatory disorders involving administration of (I) or its salt, in combination with at least one additional anti-inflammatory agents selected from selective COX-2 inhibitors, interleukin-1 **antagonists**, dihydroorotate synthase **inhibitors**, p38 MAP kinase **inhibitors**, **tumor necrosis** factor(**TNF**)- alpha **inhibitors** and **TNF**- alpha antibody or protein sequestration agents; and

(b) an article of manufacture comprising: a container (c1) containing a pharmaceutical composition (c2), and a package insert (c3) stating use of (c2) optionally in combination with a second therapeutic agent for the treatment of an inflammatory disorder. (c2) Comprises (I) or its salt.

ACTIVITY - Antiinflammatory; Antimicrobial; Ophthalmological; Hepatotropic; Antiallergic; Antiasthmatic; Anabolic; Eating-Disorders-Gen.; Antiarteriosclerotic; Dermatological; Immunosuppressive; Vasotropic; Immunomodulator; Cardiovascular-Gen.; Muscular-Gen.; Respiratory-Gen.; Anticoagulant; Antiulcer; Antipyretic; Antigout; Hemostatic; Anti-HIV; Antiarthritic; Antibacterial; Neuroprotective; Osteopathic; Antipsoriatic, Uropathic; Antirheumatic; Cytostatic; Cerebroprotective; Gastrointestinal-Gen.; Antiulcer.

MECHANISM OF ACTION - **Matrix metalloproteinase**-12 (**MMP**-12) **inhibitor**; **Tumor necrosis** factor- **alpha converting** enzyme (**TACE**) **inhibitor**; Aggrecanase **inhibitor**. Test details are described, but no results for specific compounds given. In general, (I) showed Ki value of at most 10 mu M.

USE - For treatment of inflammatory disorder, a condition or disease mediated by MMPs, TACE, aggrecanase (including acute infection, acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurysm, aortic aneurysm, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Behcet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and

tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis (claimed).

ADVANTAGE - The compounds exhibit selectivity for MMP and TACE, hence are potent MMP-12 inhibitors; eliminate undesirable tissue destruction found in variety of human diseases; can be manufactured economically; and provide effective treatment for wide variety of diseases e.g. respiratory diseases and metastatic diseases.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D02; B06-F01; B06-H; B07-D09; B14-A01; B14-A02B1; B14-C01; B14-C02; B14-C03; B14-C04; B14-C06; B14-C09; B14-D03; B14-D05C; B14-D06; B14-D07C; B14-E08; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F04; B14-F05; B14-F07; B14-F08; B14-G02; B14-H01; B14-J05; B14-K01; B14-K01A; B14-L06; B14-L07; B14-N01; B14-N03; B14-N06B; B14-N07; B14-N12; B14-N16; B14-N17; B14-S01; B14-S05; B14-S06

TECH UPTX: 20040511

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The hydantoin heterocycles are synthesized by methods as described in Matthews J, and Rivero R. A, J. Org. Chem. 1997, 62, 6090 - 6092.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Article: The article additionally comprises another container containing (c1) and (c2); and (c3) is located within or outside of the another container.

ABEX UPTX: 20040511

SPECIFIC COMPOUNDS - 14 Compounds are specifically claimed as (I), e.g. N-(2-(2,5-dioxoimidazolidin-4-yl)phenyl)-4-((2-**methylquinolin**-4-yl)methoxy)benzamide trifluoroacetate.

ADMINISTRATION - Dosage is 0.001 - 1000 (preferably 0.01 - 100, especially 1 -20) mg/kg for oral administration; and is 1 - 10 mg/kg/minute for intravenous administration during constant rate infusion. Administration is also by topical (e.g. transdermal), intranasal or parenteral route.

EXAMPLE - To a solution of 2-aminobenzyl alcohol (0.5 g) in dichloromethane (DCM)/10% NaHCO3 (1:1, 50 ml) was added 4-((2-methyl-4-**quinolinyl**)methoxy)benzoyl chloride (1.5 g). After stirring for 24 hours, the reaction mixture was filtered, and the resultant residue was washed and dried to give 2-(4-((2-methyl-4-**quinolinyl**)methoxy)benzoylamino)benzyl alcohol (Ia). A reaction mixture of (Ia) (398 mg) in DCM/dimethyl formamide (DMF) (1:1, 50 ml) and Dess-Martin periodinane (1 g) was stirred for 18 hours, and then extracted from 1N NaOH with EtOAc. After work up, 2-(4-((2-methyl-4-**quinolinyl**)methoxy)benzoylamino)benzaldehyde (Ib) was obtained. A solution of (Ib) (396 mg) in ethanol/water (1:1, 50 ml) was treated with ammonium carbonate (960 mg) and potassium cyanide (130 mg) at 80 degrees C for 24 hours; and worked up to give N-(2-(2,5-dioxoimidazolidin-4-yl)phenyl)-4-((2-**methylquinolin**-4-yl)methoxy)benzamide trifluoroacetate (47 mg).

DEFINITIONS - Full Definitions:

E1 = CRaRa1;

R1 = Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkenylene-Q, (E1)tO(E1)s-Q, (E1)tNRa(E1)s-Q, (E1)rC(O)(E1)s-Q, -(E1)rC(O)O(E1)s-Q, (E1)tOC(O)(E1)s-Q, -(E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)-Q, (E1)tNRaC(O)(E1)-Q, (E1)tOC(O)O(E1)s-Q, (E1)tOC(O)NRa(E1)s-Q, (E1)tNRaC(O)O(E1)s-Q, (E1)tNRaC(O)NRa(E1)s-Q, (E1)tS(E1)s-Q, (E1)tS(O)(E1)s-Q, (E1)rS(O)2(E1)s-Q, (E1)S(O)2NRa(E1)s-Q, (E1)tNRaSO2(E1)s-Q or (E1)tNRaSO2NRa(E1)s-Q;

L = bond, CO, CR2R3;
R2 = Q1, 1-6C alkylene-Q1, 2-6C alkenylene-Q1, 2-6C alkenylene-Q1, (E1)rO(E1)s-Q1, (E1)rNRa(E1)s-Q1, (E1)rC(O)(E1)s-Q1, (E1)rC(O)O(E1)s-Q1, (E1)rOC(O)(E1)s-Q1, (E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)s-Q1, (E1)rNRaC(O)(E1)s-Q1, (E1)rOC(O)O(E1)s-Q1, (E1)rOC(O)NRa(E1)s-Q1, (E1)rNRaC(O)NRa(E1)s-Q1, (E1)2rS(O)p(E1)s-Q1, (E1)rSO2NRa(E1)s-Q1, (E1)rNRaSO2(E1)s-Q1 or (E1)rNRaSO2NRa(E1)s-Q1;
R3 = Q, 1-6C alkylene-Q, 2-6C alkenylene-Q, 2-6C alkenylene-Q, (E1)rO(E1)s-Q, (E1)rNRa(E1)s-Q, (E1)rC(O)(E1)s-Q, -(E1)rC(O)O(E1)s-Q, (E1)rC(O)NRaRa1, (E1)rC(O)NRa(E1)s-Q, (E1)rNRaC(O)(E1)s-Q, (E1)rS(O)p(E1)s-Q, (E1)rS(O)2NRa(E1)s-Q or (E1)rNRaSO2(E1)s-Q;
Q = 3-13C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, S, or S(O)p) (both optionally substituted with 1 - 4 Rd), H, CHF2, CH2F or CF3;
Q1 = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, NR7, O or S(O)p) (both optionally substituted with 1 - 4 Rd) or H;
Z'a = 5 - 6-membered (hetero)aryl (optionally containing 1 - 3 N, NR7, O or S(O)p) or (hetero)aryl (optionally fused to 5 - 6 membered carbocycle or heterocycle optionally containing 1 - 2 N, NR7, O or S(O)p, and 0 - 2 double bonds) (both optionally substituted by 1 - 3 R6);
R11 = W'-U'-X-Y'-Z-Ua-Xa-Ya-Za;
W' = (E1)m, 2-3C alkenylene or 2-3C alkynylene;
U' = O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p or NRa1SO2NRa1;
X = absent, 1-3C alkylene, 2-3C alkenylene or 2-3C alkynylene;
Y, Ya = absent, O, NRa1, S(O)p or C(O);
Z = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted with 1 - 5 Rb);
Ua = absent, O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p or NRa1S(O)2NRa1;
Xa = absent, 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;
Za = 3-13C carbocycle or 5 - 14 membered heterocycle (containing 1 - 4 N, O or S(O)p) (both optionally substituted with 1 - 5 Rc);
Ra = H, 1-6C alkyl, phenyl, or benzyl;
Ra1 , Ra3 = 2-6C alkenyl, 1-6C alkyl or 2-6C alkynyl (all optionally monosubstituted with Rc1), (CH2)r-(3 - 8-membered carbocyclic or heterocyclic ring optionally containing 1 - 2 N, NRa2, O, and S(O)p) (optionally substituted with 1 - 3 Rc1) or H;
NRaRa1 = 5 or 6 membered heterocycle (optionally containing 1 additional N, NRa2, O, or S(O)p);
Ra2 = 1-4C alkyl, phenyl, or benzyl;
Rb = 1-6C alkyl (optionally monosubstituted with Rc1, -SRa, T1, CHF2, CH2F, or phenyl;
T1 = -ORa, halo, =O, CN, NO2, -NRaRa1, -C(O)Ra, -C(O)ORa, -C(O)NRaRa1, -C(S)NRaRa1, -NRaC(O)NRaRa1, -OC(O)NRaRa1, -NRaC(O)ORa, S(O)2NRaRa1, -NRaS(O)2Ra3, -NRaS(O)2NRaRa1, -OS(O)2NRaRa1, -S(O)pRa3, CF3 or -CF2CF3;
Rc = 1-6C alkyl, 2-6C alkenyl, (E1)r-3-10C carbocycle, or (E1)r-5 - 14-membered heterocycle (containing 1 - 4 N, O, and S(O)p) (all optionally mono- or di-substituted with Rc1), H, halo, =O, CN, NO2, CF3, -CF2CF3, CH2F, CHF2, -(E1)rORa, -(E1)rNRaRa1, -(E1)rC(=NCN)NRaRa1, -(E1)rC(=NRa)NRaRa1, -(E1)rC(=NORa)NRaRa1, -(E1)rC(O)NRaOH, -(E1)rC(O)Ra1, (E1)rC(O)ORa1, -(E1)rC(S)ORa1, -(E1)rC(O)NRaRa1, -(E1)rNRaC(O)Ra1, -(E1)rC(S)NRaRa1, -(E1)rOC(O)NRaRa1, -(E1)rNRaC(O)ORa1, (E1)rNRaC(O)NRaRa1, -(E1)rS(O)pRa3, (E1)rSO2NRaRa1, (E1)rNRaSO2Ra3, or (E1)rNRaSO2NRaRa1;
CRcRc = 3 - 8 membered carbocyclic or heterocyclic spiro ring (optionally containing 1 - 4 O, N, and S(O)p, and 1 - 2 double bonds; and optionally mono- or di-substituted with Rc1);

CRc+CRc = 5 - 7 membered carbocyclic or heterocyclic ring D (optionally containing 1 - 2 O, N, and S(O)p, and 1 - 3 double bonds; and optionally mono- or di-substituted with Rc1);
Rc1 = H, 1-4C alkyl, -ORa, halo, =O, CF3, CN, NO2, -C(O)Ra, -C(O)ORa, -C(O)NRaRa, or -S(O)pRa;
Rd = 1-6C alkyl, T1, 3-10C carbocycle, or 5 - 14 membered heterocycle (containing 1 - 4 N, O, and S(O)p);
Re = 3-10C carbocycle or 5 - 10 membered heterocycle containing 1 - 4 N, O, and S(O)p (both optionally mono- or di-substituted with Rc1), H, 1-6C alkyl, 1-6C alkoxy, phenoxy or benzoxy;
R4, R5 = H, 1-4C alkyl, 2-4C alkenyl, or 2-4C alkynyl;
R6 = T2, H, halo, =O, CN, NO2, CF3, -CF2CF3, (E1)rORa, -(E1)rNRaRa1, (E1)rC(O)NRaOH, (E1)rC(O)Ra, -(E1)rC(O)-(E1)sRe, (E1)rC(O)ORa1, (E1)rC(S)ORa1, -(E1)rC(O)NRaRa1, (E1)rNRaC(O)Ra1, (E1)rC(S)NRaRa1, -(E1)rOC(O)NRaRa1, (E1)rNRaC(O)ORa1, (E1)rNRaC(O)NRaRa1, (E1)rS(O)pRa3, -(E1)rSO2NRaRa1, (E1)rNRaSO2Ra3, or (E1)rNRaSO2NRaRa1;
T2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (E1)r-3-10C carbocycle or (E1)r-5 - 10-membered heterocycle (containing 1 - 4 N, O, and S(O)p) (all optionally mono- or di-substituted with Rc1);
R7 = H, (E1)tNRaRa1, (E1)rC(O)NRaOH, -(E1)r C(O)(E1)sRe, (E1)rC(O)ORa1, (E1)rC(S)ORa1, (E1)r C(O)NRaRa1, (E1)tNRaC(O)Ra1, (E1)rC(S)NRaRa1, (E1)tOC(O)NRaRa1, (E1)tNRaC(O)ORa1, (E1)tNRaC(O)NRaRa1, (E1)rS(O)pRa3, -(E1)rSO2NRaRa1, (E1)tNRaSO2Ra3, (E1)tNRaSO2NRaRa1 or T2;
m = 0 - 3;
p = 0 - 2;
r, s = 0 - 4; and
t = 1 - 4.
Provided that:
(1) when L is a bond, CHR2 or CHR3, and Z is phenyl, then Za is other than phenyl;
(2) when L is a bond or CH2, and Z is phenyl or naphthyl, then Za is other than a 5 or 6-membered heteroaryl or a **hydantoin** moiety;
(3) when L is a bond, Z is phenyl, -Ua-Xa-Ya- forms 1-2C alkylene, and Za is benzimidazolyl, then Rc is other than C(O)ORa1;
(4) when Z is benzo(1,4)oxazinyl, pyrrolidinyl, piperidinyl or azepanyl, then -Ua-Xa-Ya- forms other than a bond or 1-4C alkylene;
(5) when Z is 2H-benzopyranone, then Za is other than a galactopyranosyloxy moiety;
(6) when L is a bond, Z is other than thiadiazinyl; and
(7) when CRcRc forms 3 - 8 membered ring, then the ring contains other than S-S, O-O, or S-O bond; and
(8) combination of U, Y, Z, Ua, Ya, and Za is other than N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p, S(O)p-S(O)p group.

L51 ANSWER 5 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-289959 [28] WPIX
DOC. NO. CPI: C2003-075289
TITLE: New bicyclic **hydroxamate** derivatives are **inhibitors** of **matrix metalloproteinases** and/or **TNF-alpha converting** enzyme, useful for treating e.g. inflammatory disorders.
DERWENT CLASS: B02
INVENTOR(S): DUAN, J; SHEPPECK, J E; SHEPPECK, J
PATENT ASSIGNEE(S): (BRIM) BRISTOL-MYERS SQUIBB CO PATENT DEPT; (DUAN-I) DUAN J; (SHEP-I) SHEPPECK J E; (BRIM) BRISTOL-MYERS SQUIBB PHARMA CO; (BRIM) BRISTOL-MYERS SQUIBB CO
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003016248	A2	20030227	(200328)*	EN	102	C07C000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW						
US 2003130257	A1	20030710	(200347)			A61K031-553
US 6770647	B2	20040803	(200451)			C07D471-04
AU 2002324716	A1	20030303	(200452)			C07C000-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003016248	A2	WO 2002-US26018	20020815
US 2003130257	A1 Provisional	US 2001-313052P	20010817
		US 2002-219426	20020815
US 6770647	B2 Provisional	US 2001-313052P	20010817
		US 2002-219426	20020815
AU 2002324716	A1	AU 2002-324716	20020815

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002324716	A1 Based on	WO 2003016248

PRIORITY APPLN. INFO: US 2001-313052P 20010817; US 2002-219426 20020815

INT. PATENT CLASSIF.:

MAIN: A61K031-553; C07C000-00; C07D471-04

SECONDARY: A61K031-4985; A61K031-519; A61K031-538; A61K031-542; A61K031-55; A61K031-5513; A61P009-10; A61P037-08; C07D487-04

BASIC ABSTRACT:

WO2003016248 A UPAB: 20031125

NOVELTY - Bicyclic **hydroxamate** derivatives (I) are new.

DETAILED DESCRIPTION - Bicyclic **hydroxamate** derivatives of formula (I), and their salts, are new.

A = -C(O)NHOH, -C(O)NHOR5, -C(O)NHOR6, -N(OH)COR5, N(OH)CHO or -CH2SH;

B = a 5-7 membered heterocyclic ring including B1 and B2, optionally substituted with R2;

B1, B2 = 0-3C and 0-1 heteroatoms (O, N or S(O)p), optionally substituted with carbonyl;

C = a 5-10 membered aromatic ring comprising 1-9C and 0-4 heteroatoms (O, N or S(O)p); optionally substituted with R3 and R4;

R1 = U-X-Y-Z-Ua-Xa-Ya-Za;

U = C(O), C(O)O, C(O)NR1a, S(O)p or S(O)pNR1a;

X = absent or 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;

Y = absent or O, NR1a, S(O)p or C(O);

Z = 3-13C carbocycle substituted with 0-5Rb; or 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rb;

Ua = e.g. absent or O, NR1a, C(O), C(O)O, OC(O);

Xa = absent or 1 4C alkylene, 2-4C alkenylene or 2-4C alkynylene;

Ya = absent or O, NR1a, S(O)p or C(O);
Za = a 3-13C carbocycle substituted with 0-5 Rc; or a 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rc;
R2 = H; or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 Rb;
R3 = e.g. R2; 3-10C carbocycle or -(CH2)r-(3 10C carbocycle);
R4 = e.g. R2, ORa, Cl, F, Br, I, =O, CN;
Ra = H or 1-6C alkyl;
R1a = e.g. H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;
Rb = R4, CHF2, CH2F or phenyl;
Rc = e.g. H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;
R5 = 1-10C alkyl substituted with 0-2 Rb; or 1-8C alkyl substituted with 0-2 Re;
Re = phenyl or biphenyl, each substituted with 0-2 Rb;
R6 = e.g. phenyl, naphthyl, 1-10C alkyl-phenyl-(1-6C)alkyl-;
n, r = 0 4;
p = 0-2;
provided that:
(i) ring B contains other than an N-S, N-O or N-N bond;
(ii) Ua-Xa-Ya forms a spacer of 2 or more atoms, other than CH=CH- or -C triple bond C-;
(iii) U, Y, Z, Ua, Ya and Za do not combine to form N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p or S(O)p-S(O)p;
(iv) when rings B and C form tetrahydroisoquinoline, and A is C(O)NHOH, then R1 is other than (4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl, ((2 hydroxybenzoyl)amino))benzenesulfonyl, ((4 fluorophenyl)methoxy)benzenesulfonyl or ((4 methoxyphenyl)carbamate)benzenesulfonyl;
(v) when rings B and C form tetrahydro-furo(2,3-c)pyridine, A is C(O)NHOH, and U is SO2, then Z is other than phenyl;
(vi) when rings B and C form tetrahydro-1H-(1,4)-benzodiazepine, A is -C(O)NHOH, U is SO2, then Z is other than phenyl;
(vii) when U is SO2, then Ua-Xa-Ya is other than -OCH2-C triple bond C-, -NHCH2-C triple bond C-, -CH2CH2-C triple bond C- or -SCH2-C triple bond C-;
(viii) when U is SO2 and Z is phenyl, then Ua is other than OC(O).
Full definitions are given in the DEFINITIONS (Full Definitions) field.

ACTIVITY - Antiallergic; antiasthmatic; antiarteriosclerotic; dermatological; antiinflammatory; hepatotropic; virucide; vasotropic; immunomodulator; ophthalmological; antipyretic; antigout; immunosuppressive; hemostatic; anti-HIV; antiarthritic; antibacterial; osteopathic; vasotropic; uropathic; antirheumatic; cytostatic; cerebroprotective.

MECHANISM OF ACTION - Matrix metalloproteinases inhibitors; TNF-alpha converting enzyme inhibitors; aggrecanase inhibitors.

In tests to determine MMP inhibitory activity, test compounds (I) had Ki values at most 10 mu M.

USE - For treating conditions or diseases mediated by matrix metalloproteinases (MMPs), TNF-alpha converting enzyme (TACE) and/or aggrecanase; particularly acute infection, acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Behcet's syndrome, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid

withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post ischemic reperfusion injury, psoriatic arthritis, pulmonary emphysema, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis or Wegener's granulomatosis (claimed).

Inflammatory disorders can be treated by administration of (I) in combination with 1 or more antiinflammatory agents selected from selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF- alpha inhibitors, THF- alpha sequestration agents, and methotrexate (claimed).

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B14-A01; B14-A02B1; B14-B04A; B14-C02; B14-C03; B14-C04; B14-C09A; B14-C09B; B14-D07C; B14-E08; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F05; B14-F07; B14-F08; B14-G02A; B14-G02D; B14-H01; B14-J01; B14-K01; B14-K01A; B14-N03; B14-N06B; B14-N12; B14-N16; B14-N17; B14-N17C; B14-S01

TECH UPTX: 20031125

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be prepared e.g. by treating a methyl ester of formula (II) with hydroxylamine under basic conditions to give a compound of formula (IA).

ABEX UPTX: 20031125

SPECIFIC COMPOUNDS - 10 Compounds (I) are specifically claimed, e.g. N-hydroxy-6-((4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8-tetrahydro-1,6 naphthyridine-7-carboxamide; and N-hydroxy-5-((4-(2-methyl-4 quinolinyl)methoxy)phenyl)sulfonyl)-4,5,6,7 tetrahydro(1,3)thiazolo(4,5-c)pyridine-6-carboxamide.

ADMINISTRATION - Administration is by conventional routes. Daily oral dosage is 0.001-1000 (preferably 1-20) mg/kg. Intravenous dosage is 1-10mg/kg/minute during constant rate infusion.

EXAMPLE - Diethyl 6-acetyl-5,8-dihydropyrido(3,4-b)pyrazine 7,7(6H)-dicarboxylate (0.557mmol) was dissolved in 6M HCl (3ml) and refluxed for 1.5 hours. The mixture was cooled, concentrated and taken up in saturated HCl in MeOH (10ml). After refluxing overnight, the mixture was concentrated to give the crude amino ester HCl salt. This was taken up in MeOH (10ml) and hydrogen chloride was bubbled through the solution for 30 minutes. The mixture was stirred overnight, then concentrated, dried, and dissolved in DMF (2ml).

(4-((2-Methyl-4 quinolinyl)methoxy)phenyl)acetic acid (205mg), diisopropylethylamine (486microl) and PyBOP (377mg) were added. After stirring overnight, the mixture was partitioned between EtOAc and saturated NaHCO3 and separated. The organic phase was dried, filtered, concentrated and passed through a silica plug. Purification of the residue by HPLC gave methyl 6-((4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8-tetrahydropyrido(3,4 b)pyrazine-7-carboxylate.

An anhydrous solution of hydroxylamine in MeOH (1.5ml, 1.64M) was added to the bis-TFA salt of this compound (62mg). After 30 minutes, the mixture was concentrated and purified by HPLC to give N-hydroxy-6-((4-((2

methyl-4-quinolinyl)methoxy)phenyl)acetyl)-5,6,7,8 tetrahydropyrido(3,4-b)pyrazine-7-carboxamide (25mg, 37%) as the TFA salt after lyophilization.
DEFINITIONS - Full Definitions:
A = -C(O)NHOH, -C(O)NHOR5, -C(O)NHOR6, -N(OH)COR5, N(OH)CHO or -CH2SH;
B = a 5-7 membered heterocyclic ring including B1 and B2, optionally substituted with R2;
B1, B2 = 0-3C and 0-1 heteroatoms (O, N or S(O)p), optionally substituted with carbonyl;
C = a 5-10 membered aromatic ring comprising 1-9C and 0-4 heteroatoms (O,N or S(O)p); optionally substituted with R3 and R4;
R1 = U-X-Y-Z-Ua-Xa-Ya-Za;
U = C(O), C(O)O, C(O)NR1a, S(O)p or S(O)pNR1a;
X = absent or 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;
Y = absent or O, NR1a, S(O)p or C(O);
Z = 3-13C carbocycle substituted with 0-5Rb; or 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rb;
Xa = absent or 1 4C alkylene, 2-4C alkenylene or 2-4C alkynylene;
Ya = absent or O, NR1a, S(O)p or C(O);
Za = a 3-13C carbocycle substituted with 0-5 Rc; or a 5-14 membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-5 Rc;
R2 = H; or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 Rb;
Ra = H or 1-6C alkyl;
Rb = R4, CHF2, CH2F or phenyl;
R5 = 1-10C alkyl substituted with 0-2 Rb; or 1-8C alkyl substituted with 0-2 Re;
Re = phenyl or biphenyl, each substituted with 0-2 Rb;
n, r = 0 4;
p = 0-2;
Ua = absent or O, NR1a, C(O), C(O)O, OC(O), C(O)NR1a, NR1aC(O), OC(O)O, OC(O)NR1a, NR1aC(O)O, NR1aC(O)NR1a, S(O)p, S(O)pNR1a, NR1aS(O)p or NR1aSO2NR1a;
R3 = R2; 3-10C carbocycle or -(CH2)r-(3 10C carbocycle), each substituted with 0-2 Rb; or -(CH2)r-(5 10)membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-2 Rb;
R4 = R2, ORa, Cl, F, Br, I, =O, CN, NO2, NRaR1a, C(O)Ra, C(O)ORa, C(O)NRaR1a, NRaC(O)Ra, C(S)NRaR1a, NRaC(O)NRaR1a, OC(O)NRaR1a, NRaC(O)ORa, S(O)2NRaR1a, NRaS(O)2Ra3, NRaS(O)2NRaR1a, OS(O)2NRaR1a, NRaS(O)2Ra3, S(O)pRa3, CF3, OCF3 or CF2CF3;
R1a, Ra3 = H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-1 Rc1; or -(CH2)r-(3-8)membered carbocyclic or heterocyclic ring comprising C and 0-2 ring heteroatoms (N, NRa2, O or S(O)p) substituted with 0-3 Rc1; or Ra and R1a together with N to which they are attached may form a 5 or 6-membered heterocycle comprising C and 0-1 additional heteroatoms (N, NRa2, O or S(O)p);
Ra2 = 1-4C alkyl, phenyl or benzyl;
Rc = H; 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl, each substituted with 0-2 Rc1; ORa, Cl, F, Br, I, =O, CN, NO2, CF3, CF2CF3, CH2F, (CRaR1a)nNRaR1a, (CRaR1a)nC(=NCN)NRaR1a, (CRaR1a)nC(=NRa)NRaR1a, (CRaR1a)nC(O)NRaOH, (CRaR1a)nC(O)R1a, (CRaR1a)nC(O)OR1a, (CRaR1a)nC(S)OR1a, (CRaR1a)nC(O)NRaR1a, (CRaR1a)NRaC(O)R1a, (CRaR1a)nC(S)NRaR1a, (CRaR1a)nOC(O)NRaR1a, (CRaR1a)nNRaC(O)OR1a, (CRaR1a)nNRaC(O)NRaR1a, (CRaR1a)nS(O)pRa3, (CRaR1a)nSO2NRaR1a, (CRaR1a)nNRaSO2Ra3, (CRaR1a)nNRaSO2NRaR1a; -C(RaR1a)n-(3-10C)carbocycle substituted with 0-2 Rc1; or -(CRaR1a)n-(5-14)membered heterocycle comprising C and 1-4 heteroatoms (N, O or S(O)p) substituted with 0-2 Rc1;
Rc1 = H, 1-4C alkyl, ORa, Cl, F, Br, I, =O, CF3, CN, NO2, C(O)Ra, C(O)ORa, C(O)NRaRa or S(O)pRa;

R6 = phenyl, naphthyl, 1-10C alkyl-phenyl-(1 6C)alkyl-, 3-11C cycloalkyl, 1-6C alkylcarbonyloxy-(1-3C)alkyl, 1 6C alkylcarbonyloxy-(1-3C)alkyl, 2-10C alkoxycarbonyl, 3-6C cycloalkylcarbonyloxy-(1-3C)alkyl, 3-6C cycloalkoxycarbonyloxy-(1 3C)alkyl, 3-6C cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-(1-3C)alkyl, phenylcarbonyloxy(1-3C)alkyl, 1 6C alkoxy-(1-6C)alkylcarbonyloxy-(1-3C)alkyl, (5-(1-5C alkyl)-1,3 dioxa-cyclopenten-2-one-yl)methyl, (5-(Ra)-1,3-dioxa-cyclopenten 2-one-yl)methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, 1 10C alkyl-NR7R7a, -CH(R8)OC(=O)R9 or -CH(R8)OC(=O)OR9;
R7, R7a = H, 1-10C alkyl, 2-6C alkenyl, 3-6C cycloalkyl-(1 3C)alkyl or phenyl-(1-6C)alkyl;
R8 = H or 1-4C linear alkyl;
R9 = H; 1-8C alkyl or 3-8C cycloalkyl, each substituted with 12 Rf; or phenyl substituted with 0-2 Rb;
Rf = 1-4C alkyl, 38C cycloalkyl, 1-5C alkoxy, or phenyl substituted with 0-2 Rb.
provided that:
(i) ring B contains other than an N-S, N-O or N-N bond;
(ii) Ua-Xa-Ya forms a spacer of 2 or more atoms, other than CH=CH- or -Ctriple bondC-;
(iii) U, Y, Z, Ua, Ya and Za do not combine to form N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p or S(O)p-S(O)p;
(iv) when rings B and C form tetrahydroisoquinoline, and A is C(O)NHOH, then R1 is other than (4-((2-methyl-4 quinolinyl)methoxy)phenyl)acetyl, ((2 hydroxybenzoyl)amino))benzenesulfonyl, ((4 fluorophenyl)methoxy)benzenesulfonyl or ((4 methoxyphenyl)carbamate)benzen esulfonyl;
(v) when rings B and C form tetrahydro-furo(2,3-c)pyridine, A is C(O)NHOH, and U is SO2, then Z is other than phenyl;
(vi) when rings B and C form tetrahydro-1H-(1,4-benzodiazepine, A is -C(O)NHOH, U is SO2, then Z is other than phenyl;
(vii) when U is SO2, then Ua-Xa-Ya is other than -OCH2-Ctriple bondC-, -NHCH2-Ctriple bondC-, -CH2CH2-Ctriple bondC- or -SCH2-Ctriple bondC-;
(viii) when U is SO2 and Z is phenyl, then Ua is other than OC(O).

L51 ANSWER 6 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-080580 [08] WPIX
DOC. NO. CPI: C2004-033220
TITLE: New acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl hydroxamic acids useful for treating graft rejection, HIV, atherosclerosis, restenosis, angiogenesis, tumor metastasis.
DERWENT CLASS: B05
INVENTOR(S): ALBRIGHT, J D; CHEN, J M; DU, X; LEVIN, J I; ZASK, A
PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO; (AMHP) WYETH HOLDINGS CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2003208066	A1	20031106	(200408)*		36	C07D279-02
US 6946473	B2	20050920	(200562)			C07D471-04

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2003208066	A1	Provisional	US 1999-198221P	19990127
		Cont of	US 2000-492978	20000127
			US 2003-390515	20030317

US 6946473	B2 Provisional	US 1999-198221P	19990127
	Cont of	US 2000-492978	20000127
		US 2003-390515	20030317

PRIORITY APPLN. INFO: US 1999-198221P 19990127; US 2000-492978 20000127; US 2003-390515 20030317

INT. PATENT CLASSIF.:
MAIN: C07D279-02; C07D471-04
SECONDARY: A61K031-437; A61P019-02; C07D487-02; C07D491-02; C07D498-02; C07D498-04; C07D513-04

BASIC ABSTRACT:

US2003208066 A UPAB: 20040202

NOVELTY - Acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl **hydroxamic** acids are new.

DETAILED DESCRIPTION - Acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl **hydroxamic** acids of formulae (I) - (IV) or their salts are new.

W and X = C or N;

P1 and Q = -N(R5)-G-L-Z-C(R6)(R7)-C equivalent to C-R8 or -C(O)-NHOH;

Y = C, N, O or S;

G = SO2 or P(O)R4;

L = phenyl, naphthyl or heteroaryl;

Z = O, NH, S or CH2;

A = phenyl ring or heteroaryl ring of formulae (i) - (iii), pyrazine or pyridine;

K1 = O, NR9 or S;

R5 = H or 1-6C alkyl;

R6 and R7 = H, 1-6C alkyl, CN or CCH;

R8 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, phenyl, naphthyl or 5 - 10 membered heteroaryl (containing 1 - 3 N, NR9, O or S);

R9 = H, 1-6C alkyl, 3-6C cycloalkyl or phenyl.

Provided that:

(1) when P1 is -N(R5)-G-L-Z-C(R6)(R7)-C equivalent to C-R8, then Q is -C(O)-NHOH or vice-versa;

(2) at least one of W, X and Y is other than C; and

(3) G and Z are not bonded to adjacent atoms of L

An INDEPENDENT CLAIM is included for sulfonic acid derivatives of formula (XII) and (XIII).

R8a = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, phenyl, naphthyl, 5 - 10 membered heteroaryl (containing 1 - 3 N, NR9, O or S), or 5 - 9 membered heterocycloalkyl (containing 1 or 2 N, NR9, O or S);

J = F, Cl, Br, 1,2,4-triazolyl, benzotriazolyl or imidazolyl.

ACTIVITY - Antirheumatic; Antiarthritic; Immunosuppressive; Immunomodulator; Antiinflammatory; Antipyretic; Antidiabetic; Cardiant; Anti-HIV; CNS-Gen.; Gastrointestinal-Gen.; Antiarteriosclerosis, Vasotropic; Antiangiogenic; Neuroprotective; Cytostatic; Osteopathic; Dermatological; Ophthalmological; Hepatotropic; Nephrotropic; Antibacterial; Antiulcer; Vulnerary.

MECHANISM OF ACTION - **TNF- alpha converting** enzyme (**TACE**) **inhibitor**; **Matrix metalloproteinase** (**MMP**-1/9/13) **inhibitor**; Angiogenesis **inhibitor**.

The efficacy of 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-**quinoline**-3-carboxylic acid hydroxyamide (T1) to **inhibit TACE** was evaluated by incubating T1 (10 mu l)

with **TACE** (10 mu l) in a solution containing Tris buffer (70 mu l) and 10% glycerol at room temperature for 10 minutes. A fluorescent peptidyl substrate (100 mu M) was then added to the reaction mixture. The reaction was evaluated by measuring the fluorescence. (T1) showed an IC50 value of 17 nM.

USE - For **inhibiting** pathological changes mediated by **TNF- alpha converting** enzyme (**TACE**); for treating rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, HIV (claimed), atherosclerosis, restenosis, skin aging, angiogenesis, corneal ulceration, arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, aneurysmal aortic disease, demyelinating diseases of central nervous system, cirrhosis of the liver, glomerular diseases of kidney, premature rupture of fetal membranes, age related macular degeneration, diabetic retinopathy, Sjogren's syndrome, ocular tumor, ocular angiogenesis.

ADVANTAGE - (I) exhibit enhanced levels of the **inhibition** of the **TACE** activity and selectivity over **matrix metalloproteinase** (e.g. **MMP**-1).

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B05-B01E; B06-H; B14-A01; B14-A02B1; B14-C03; B14-C04; B14-C06; B14-C09; B14-E08; B14-E10; B14-F01; B14-F02; B14-F07; B14-G02; B14-G03; B14-H01B; B14-J01; B14-N01; B14-N03; B14-N10; B14-N12; B14-N17; B14-S04

TECH UPTX: 20040202

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where Q is -C(O)-NHOH, P1 is -N(R5)-G-L-Z-C(R6)(R7)-Cequivalent toC-R8 and L is phenyl) involves converting carboxylic acid of formula (ia) into corresponding acid chloride or anhydride; or by reacting it with a peptide coupling agent, followed by reaction with hydroxylamine derivative to give (ib) and deprotection.

R30 = tert-butyl, benzyl, trialkylsilyl or other masking group.

ABEX UPTX: 20040202

SPECIFIC COMPOUNDS - 4((4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide, 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-1,3-dimethyl-1H-pyrazolo(3,4-b)pyridine-5-carboxylic acid hydroxyamide, 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-3-methyl-isothiazolo(5,4-b)pyridine-5-carboxylic acid hydroxyamide, 8-bromo-4(((4-(2-butynyloxy)phenyl)sulfonyl)-(methyl)amino)-N-hydroxy-3-quinolinecarboxamide and 4-((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-3-methyl-isoxazolo(5,4-b)pyridine-5-carboxylic acid hydroxyamide are specifically claimed as (I).

ADMINISTRATION - Administration is by oral, intranasal, intramuscular, intraperitoneal, subcutaneous, intrabronchial or transdermal route. No dosage given.

EXAMPLE - To a solution of 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid ethyl ester (0.82 g) in tetrahydrofuran (THF) (10 ml) and methanol (5 ml) was added 1N NaOH (2.15 ml) and the resultant mixture was refluxed for 3 hours. The resultant residue was triturated with ether to give 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylate salt (A1). To a solution of 2 M oxalyl chloride in dichloromethane (1.67 ml) was added dimethylformamide (DMF) (0.258 ml) and the reaction was stirred at 0degreesC for 15 minutes. A solution of (A1) (0.75 g) in DMF was added

to the reaction mixture and stirred for 1 hour at room temperature. The resultant mixture was poured into a mixture of triethylamine (1.395 ml), THF (3 ml) and 50% aqueous solution of hydroxylamine (0.408 ml). The reaction was warmed at room temperature overnight and worked up to give 4((4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide.

DEFINITIONS - Preferred Definitions:
W and X = C;
P1 = -N(R5)-G-L-Z-C(R6)(R7)-Cequivalent toC-R8;
Q = -C(O)-NHOH;
Y = N;
G = SO2;
L = phenyl substituted at 1- and 4-positions by G and Z respectively;
Z = O;
R6 and R7 = H;
R8 = -CH2OH or methyl.

L51 ANSWER 7 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-456157 [43] WPIX
CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2001-656404 [75]; 2002-146947 [19]
DOC. NO. CPI: C2003-121212
TITLE: New ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids useful as **matrix metalloproteinase inhibitors** for treatment of diseases e.g. arthritis.
DERWENT CLASS: B05 D21
INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A
PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y; (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN CYANAMID CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2002132826	A1	20020919	(200343)*		39	A61K031-497
US 6534491	B2	20030318	(200343)			C07D471-02

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002132826	A1	US 2000-734146	20001211
US 6534491	B2 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
	Div ex	US 1998-59554	19980414
		US 2000-734146	20001211

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6534491	B2 Div ex	US 6228869

PRIORITY APPLN. INFO: US 2000-734146 20001211; US 1996-28505P 19961016; US 1997-944188 19971006; US

1998-55856 19980406; US
1998-59554 19980414

INT. PATENT CLASSIF.:
MAIN: A61K031-497; C07D471-02
SECONDARY: A61K031-415; A61K031-44; A61K031-47; C07D207-00; C07D217-00; C07D221-02; C07D491-02; C07D498-02; C07D513-02; C07D515-02

BASIC ABSTRACT:
US2002132826 A UPAB: 20030707
NOVELTY - Ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids (I) - (III) or their salts, are new.
DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids of formula (I) - (III) or their salts, are new:
A = 5-6 membered phenyl or heteroaryl ring which may contain 0 - 2 heteroatoms selected from N, O or S (both optionally mono- to tri-substituted by R1);
R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, -(CH2)n-Z, -OR2, -CN, COR2, 1-4C perfluoroalkyl, -CONR2R3, -S(O)xR2, -OP(O)(OR2)OR3, PO(OR2)OR3, OC(O)NR2R3, COOR2, -CONR2R3, SO3H, NR2R3, NR2COR3, NR2COOR3, SO2NR2R3, NO2, N(R2)SO2R3, NR2CONR2R3, NR2C(=NR3)NR2R3, SO2NHCOR4, CONHSO2R4, tetrazol-5-yl, SO2NHCN, SO2NHCONR2R3 or Z;
x = 0 - 2;
n = 1 - 6;
R2, R3 = H or L;
L = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V';
Z = heteroaryl (optionally fused with phenyl and containing 5 - 6 ring atoms and 1 - 3 heteroatoms selected from N, O or S), phenyl or naphthyl (all optionally mono- to tri-substituted by R1);
V' = saturated or partially unsaturated heterocycloalkyl ring of 5 - 7 ring atoms having 1 - 3 heteroatoms of N, O or S (optionally mono- or di-substituted by R2);
R4 = L;
P, Q = -N(CH2-R5)-S(O)2-Z or -C(O)-NHOH;
R5 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V';
T, U, W, X = C or N;
Y = C, N, O or S; and
provided that:
(1) P and Q are not -N(CH2-R5)-S(O)2-Z or -C(O)-NHOH at the same time;
(2) when T and U are C, then both are optionally substituted by R1; and
(3) at least one of T, U, W, X and Y is not carbon and less than 2 of T, U, W and X are nitrogen.
ACTIVITY - Antiarthritic; Antirheumatic; Antiinflammatory; Immunosuppressive; Antipyretic; Antibacterial; Cardiant; Anti-HIV; Antiarteriosclerotic; Cytostatic; Antitumor; Vulnerary; Hepatotropic; Vasotropic; Antiulcer; Nephrotropic; Dermatological; Antidiabetic; Ophthalmological; Immunomodulator; CNS-Gen.; Osteopathic.
MECHANISM OF ACTION - **Matrix metalloproteinase** (**MMP**) (e.g. gelatinase, stromelysin and collagenase) **inhibitors**; **TNF**- **alpha converting** enzyme **inhibitors.**
Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt and (5,5'-dithiobis(2-nitrobenzoic acid)) (DTNB) were diluted together to 1 mM with a substrate buffer (50 mM HEPES, pH 7.5, 5 mM CaCl2). The stock of **MMP**-13 (collagenase) was also diluted with a substrate buffer (50 mM HEPES, pH 7.5, 5 mM CaCl2, 0.02% Brij) to a final concentration. The buffer, enzyme, vehicle or 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-

trifluoromethyl-**quinoline**-3-carboxylic acid hydroxyamide (A) and DTNB/substrate were added in this order to a 96 well plate and the increase in color was monitored spectrophotometrically, from which IC50 value was determined. (A) showed IC50 of 7 nM for **MMP**-13.

USE - For inhibiting pathological changes (e.g. atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, **MMP**-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease or periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of pre-maturity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumor, ocular angiogenesis/neovascularization and corneal graft rejection) mediated by **matrix metalloproteinase** and changes (e.g. graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory diseases of the central nervous system, inflammatory bowel disease and HIV infection) mediated by **TNF- alpha converting** enzyme (**TACE**) in a mammal (claimed).

ADVANTAGE - The compounds are **inhibitors** of **matrix metalloproteinases** (e.g. gelatinases, stromelysins and collagenases) and **TNF- alpha converting** enzyme.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B14-A02B1; B14-C03; B14-C04; B14-C09; B14-D07C; B14-E10C; B14-E11; B14-F01; B14-F01B; B14-F01G; B14-F04; B14-F07; B14-G02C; B14-H01; B14-J01; B14-J01A2; B14-N01; B14-N03; B14-N06B; B14-N10; B14-N12; B14-N17; B14-S04; B14-S06; D08-B09A3

TECH UPTX: 20030707

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The compounds are prepared by:
(1) reacting a bicyclic heteroaryl prepared from a corresponding aniline, with N-benzyl-para-methoxybenzenesulfonamide to form N,N-disubstituted sulfonamido-ester; and
(2) converting the ester.

ABEX UPTX: 20030707

SPECIFIC COMPOUNDS - 66 Compounds (I) - (III) are specifically claimed, e.g. 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide.

ADMINISTRATION - The compounds can be administered orally in a dosage of (2 - 500, preferably 2 - 50, especially 5 - 25 mg/kg), nasally or parenterally (including intramuscular, intraperitoneal, or subcutaneous injection), intranasal or intrabronchial inhalation or insufflation, rectally, transdermally or as an aerosol.

EXAMPLE - Dimethylformamide (DMF) (0.05 ml) was added to a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino-)-7-trifluoromethyl-quinoline-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml), followed by addition of 2M oxalyl chloride (1.26 ml), and the resulting mixture was

stirred at room temperature for 1 hour. Triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After this mixture was stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it in one portion and the resulting solution was warmed to room temperature and stirred for another 4 hours. Water was added to the reaction flask and 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (0.488 g, 75% yield) was collected.

DEFINITIONS - Preferred Definitions:
The compound is of formula (II).
W, X = C;
T = N;
U = C optionally substituted by R1;
P' = -N(CH2-R5)-S(O)2-Z;
Q = -C(O)-NHOH; and
T' = phenyl or pyrazole (both optionally mono- to tri-substituted by R1).

L51 ANSWER 8 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-146947 [19] WPIX
CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2001-656404 [75]; 2003-456157 [43]
DOC. NO. CPI: C2002-045527
TITLE: New ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids are useful for treating diseases implicated by metalloproteinases and **tumor necrosis** factor-alpha e.g. atherosclerosis and restenosis.
DERWENT CLASS: B05
INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A
PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y; (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN CYANAMID CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2001046989	A1	20011129	(200219)*		39	A61K031-535
US 6548524	B2	20030415	(200329)			A61K031-59

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2001046989	A1	Provisional	US 1996-28505P	19961016
		CIP of	US 1997-944188	19971006
			US 2000-734140	20001211
US 6548524	B2	Provisional	US 1996-28505P	19961016
		CIP of	US 1997-944188	19971006
		CIP of	US 1998-55856	19980406
		Div ex	US 1998-59554	19980414
			US 2000-734140	20001211

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US 1997-944188 19971006; US 2000-734140 20001211; US 1998-55856 19980406; US

1998-59554 19980414

INT. PATENT CLASSIF.:
MAIN: A61K031-535; A61K031-59
SECONDARY: C07D221-02; C07D471-02; C07D491-02; C07D498-02; C07D513-02; C07D515-02

BASIC ABSTRACT:
US2001046989 A UPAB: 20030707
NOVELTY - Ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids (B) and their salts are new.
DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic heteroaryl **hydroxamic** acids of formula (B) and their salts are new.
(B) = compound of formula (Ia), (Ib) or (Ic);
P and Q = -N-(CH2-R5)-(SO2)-Z (II) or -C(=O)-NHOH (III);
T, U, W and X = C or N;
Y = C, N, O or S;
A = phenyl or 5-6 membered heteroaryl ring (containing 0 - 2 heteroatom selected from N, O or S in addition to any heteroatoms defined by W or X and, is optionally mono-, di- or tri-substituted with R1);
Z = phenyl, naphthyl, M or M fused to phenyl (all optionally mono-, di- or tri-substituted with R1);
M = heteroaryl moiety containing 5 - 6 ring atoms and 1 - 3 heteroatoms selected from N, O or S;
V = saturated or partially saturated heterocycloalkyl ring of 5 - 7 ring atoms having 1 - 3 heteroatoms selected from N, O or S (optionally mono-, or di-substituted with R2);
R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, -(CH2)nZ, -OR2, -CN, -COR2, 1-4C perfluoroalkyl, -CONR2R3, -S(O)xR2, -OPO(OR)OR3, -PO(OR2)R3, -OC(O)NR2R3, -COOR2, -CONR2R3, -SO3H, -NR2R3, -NR2COR3, -NR2COOR3, -SO2NR2R3, -NO2, -N(R2)SO2R3, -NR2CO, NR2R3, -NR2C(=NR3)NR2R3, -SO2NHCOR4, -CONHSO2R4, -tetrazol-5-yl, -SO2NHCN, -SO2NHCONR2R3 or Z;
R2 and R3 = H or Z1;
Z1 = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl or 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;
R4 = Z1;
R5 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V;
n = 1 - 6; and
x = 0 - 2.
Provided that when T or U is carbon, either may be optionally substituted with R1; and when P is (II), then Q is (III) or when P is (III), Q is (II); and at least one of T, U, W, X and Y is not carbon and than no more than 2 of T, U, W and X are nitrogen.
ACTIVITY - Antiarteriosclerotic; vasotropic; anti-inflammatory; dermatological; osteopathic; antiarthritic; cytostatic; antirheumatic; antiulcer; vulnerary; hepatotropic; nephrotropic; nootropic; neuroprotective; antidiabetic; ophthalmological; keratolytic; immunosuppressive; antipyretic; cardiant; antibacterial; anti-HIV.
MECHANISM OF ACTION - **Tumor necrosis** factor-**alpha converting** enzyme (**TACE**) **inhibitor**; **Matrix metalloproteinases** (**MMP**) (preferably **MMP**-1, **MMP**-9 and **MMP**-13) **inhibitor.**
In tests for measuring in vivo **MMP inhibitory** action of (B), carried out on Sprague Dawley rats, 4-(pyridin-3-ylmethyl-(toluene-4-sulfonyl)-amino)-7-trifluoromethyl-**quinoline**-3-carboxylic acid hydroxyamide showed inhibition of 65% at 1 micro M concentration.
USE - For **inhibiting** pathological changes mediated by **matrix metalloproteinase** (**MMP**) and the condition mediated by **MMP** are atherosclerosis, atherosclerotic

plaque formation, **reduction** of coronary thrombosis from atherosclerotic plaque rupture, restenosis, **MMP**-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease or periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection; also for **inhibiting** pathological changes mediated by **tumor necrosis** factor (**TNF**) - **alpha converting** enzyme (**TACE**) e.g. rheumatoid arthritis, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection (all claimed).

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B14-A01; B14-A02B1; B14-C04; B14-C06; B14-C09; B14-D07C; B14-E10C; B14-E11; B14-F01B; B14-F01G; B14-F02; B14-F07; B14-G02C; B14-J01; B14-N03; B14-N10; B14-N12; B14-N16; B14-N17B; B14-N17C; B14-P03; B14-S04; B14-S06

TECH UPTX: 20021113

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (B) is prepared e.g. by reaction of 4-chloro-7-trifluoromethylquinoline-3-carboxylic acid ethyl ester with R7-NH2, and the resulting 4-(R7-amino)quinoline carboxylic acid ester is then reacted with the appropriate Z-SO2-Cl. Hydrolysis of the ester and reaction with hydroxylarine hydrochloride yields a compound of (B).

ABEX UPTX: 20021113

SPECIFIC COMPOUNDS - 66 Compounds (I) are specifically claimed e.g. 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (I').

ADMINISTRATION - The compound may be administered by intramuscular, intraperitoneal, subcutaneous, intravenous, oral, intranasal or intrabronchial inhalation or insufflation route or transdermal route. For oral route, the daily dosage is 2 - 500 (preferably 5 - 25) mg/kg.

EXAMPLE - To a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml) was added dimethyl formamide (0.05 ml) followed by 2M oxalyl chloride (1.26 ml). The resulting mixture was stirred at room temperature for 1 hour. In a flask, triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After this mixture had been stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it in one portion. The resulting solution was warmed to room temperature and stirred for 4 hours. Water was then added to the reaction flask to obtain 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide (I'; 75%).

DEFINITIONS - Preferred Definitions:
(B) = formula (Ib);

W and X = C;
U = C optionally substituted with R1;
P = formula (II);
Q = formula (III); and
A = phenyl of pyrazole ring optionally mono-, di- or tri-substituted with R1.

L51 ANSWER 9 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-656404 [75] WPIX
CROSS REFERENCE: 1999-312431 [26]; 2001-424086 [45]; 2002-146947 [19]; 2003-456157 [43]
DOC. NO. CPI: C2001-193023
TITLE: New bicyclic heteroaryl **hydroxamic** acids are **matrix metalloproteinase inhibitor** and **tumor necrosis** factor-**alpha converting** enzyme **inhibitors**, useful in the treatment of e.g. arteriosclerosis, inflammation, arthritis and tumors.
DERWENT CLASS: B02 B03
INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A
PATENT ASSIGNEE(S): (ALBR-I) ALBRIGHT J D; (DUXX-I) DU X; (GUYY-I) GU Y; (LEVI-I) LEVIN J I; (ZASK-I) ZASK A; (AMCY) AMERICAN CYANAMID CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2001025047	A1	20010927	(200175)*		40	C07D215-12
US 6498167	B2	20021224	(200303)			A61K031-56

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2001025047	A1	Provisional	US 1996-28505P	19961016
		CIP of	US 1997-944188	19971006
		CIP of	US 1998-55856	19980406
		Div ex	US 1998-59554	19980414
			US 2000-734056	20001211
US 6498167	B2	Provisional	US 1996-28505P	19961016
		CIP of	US 1997-944188	19971006
		CIP of	US 1998-55856	19980406
		Div ex	US 1998-59554	19980414
			US 2000-734056	20001211

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2001025047	A1	Div ex	US 6228869
US 6498167	B2	Div ex	US 6228869

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US
1997-944188 19971006; US
1998-55856 19980406; US
1998-59554 19980414; US
2000-734056 20001211
INT. PATENT CLASSIF.:
MAIN: A61K031-56; C07D215-12

SECONDARY: A61K031-4709; C07D215-14; C07D217-00

BASIC ABSTRACT:

US2001025047 A UPAB: 20030707

NOVELTY - Bicyclic heteroaryl **hydroxamic** acids are new.

DETAILED DESCRIPTION - Bicyclic heteroaryl **hydroxamic** acids of formula (Ia), (Ib) and (Ic) and their salts are new.

P, Q = -N(CH2-R5)-S(=O)2-Z or -C(O)-NHOH;

T, U, W, X = C or N;

Y = C, N, S or O;

A = phenyl or A' (both optionally substituted by 1-3 R1);

A' = 5-6 membered heteroaryl ring containing 0-2 N, O or S;

Z = phenyl, naphthyl, A' or A' fused to phenyl (all optionally substituted by 1-3 R1);

R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, -(CH2)nZ, -OR2, -CN, -COR2, 1-4C perfluoroalkyl, -CONR2R3, -S(O)xR2, -OPO(OR2)OR3, -PO(OR2)R3, -OC(O)NR2R3, -COOR2, -CONR2R3, -SO3H, -NR2R3, -NR2COR3, -NR2COOR3, -SO2NR2R3, -NO2, -N(R2)SO2R3, -NR2ONR2R3, -NR2C(=NR3)NR2R3, -SO2NHCOR4, -CONHSO2R4, -tetrazol-5-yl, -SO2NHCN, -SO2NHCONR2R3 or Z;

V = saturated or partially unsaturated 5-7 membered heterocycloalkyl ring containing 1-3 N, O or S (optionally substituted by 1-2 R2) ;

R2, R3 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;

R4 = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;

n = 1-6; and

x = 0-2;

provided that when T and U = C, then either may be optionally substituted by R1; at least one of T, U, W, X and Y is not C, and no more than 2 of T, U, W and X = N; and when P = -N(CH2-R5)-S(=O)2-Z, then Q = -C(O)-NHOH and vice versa.

ACTIVITY - Antiarteriosclerotic; Thrombolytic; Cardiant; Vasotropic; Osteopathic; Antiinflammatory; Cerebroprotective; Neuroprotective; Dermatological; Cytostatic; Antiarthritic; Antirheumatic; Antibacterial; Opthalmological; Antiulcer; Vulnerary; Hepatotropic; Nephrotropic; Antidiabetic; Gastrointestinal; Immunosuppressive; Anabolic; Immunomodulator; Antipyretic; Virucide; Anti-HIV.

MECHANISM OF ACTION - **Matrix metalloproteinase** (**MMP**) **inhibitor**; **Tumor necrosis** factor- **alpha** (**TNF**- **alpha**) **converting** enzyme (**TACE**) **inhibitor.**

A 2 cm piece of dialysis tubing containing **MMP**-1 (stromelysin), **MMP**-13 (collagenase) or **MMP**-9 (gelatinase) in buffer (0.5 ml) was implanted to Sprague-Dawley rat. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-**quinoline**-3-carboxylic acid hydroxyamide (I') (0.1 - 0.25 ml) was administered through a cannula in the jugular vein. Contents of the dialysis tubing was collected and enzyme activity assayed. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-**quinoline**-3-carboxylic acid hydroxyamide (I') displayed IC50 values of 46, 2 and 1 nM against **MMP**-1, **MMP**-9 and **MMP**-13 respectively.

USE - In the treatment of atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating disease of the nervous system, cirrhosis of the

liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjoegrens syndrome, myopia, ocular tumor, ocular angiogenesis/neovascularization, corneal graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure and HIV infection (all claimed).

ADVANTAGE - The compounds are long-acting and orally bioavailable.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B05-B01E; B05-B01M; B06-H; B14-A02B1; B14-C03; B14-C04; B14-C09; B14-D07C; B14-E10C; B14-E11; B14-F01B; B14-F02D; B14-F04; B14-F07; B14-G02C; B14-H01; B14-J01; B14-J05B; B14-L06; B14-N01; B14-N03; B14-N06B; B14-N10; B14-N12; B14-N17; B14-P03; B14-S01; B14-S06

TECH UPTX: 20011220

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: 11 Methods of preparing the compounds are disclosed, e.g. reacting quinoline carboxylic acid ester with an amine, and further with appropriate Z-SO2-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydrochloride forms (I).

ABEX UPTX: 20011220

SPECIFIC COMPOUNDS - 66 Compounds (I) are specifically claimed e.g. 4-((4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I').

ADMINISTRATION - Administration of (I) is 2-500, preferably 5-25 mg/kg/day orally. (I) May also be administered intramuscularly, intraperitoneally, subcutaneously, intranasally, by intrabronchial inhalation or transdermally.

EXAMPLE - To a solution of 4-chloro-8-methoxy-3-quinolinecarboxylate (2 mmol) in methanol/tetrahydrofuran (THF) (1:1) (4 ml) was added 1 N sodium hydroxide solution and the resulting mixture was stirred at 25 degrees C for 18 hours to form a carboxylic acid (A). To a solution of (A) (1.26 mmol) in dichloromethane (12.5 ml) was added dimethylformamide (0.05 ml) followed by 2 M oxalyl chloride (1.26 ml) and the mixture was stirred at room temperature for 1 hour. In a separate flask, triethylamine (2.6 ml) was added to a 0 degrees C mixture of hydroxylamine hydrochloride (350 mg) in THF (14 ml) and water (3.5 ml). After this mixture had been stirred for 15 minutes at 0 degrees C, the acid chloride solution was added to it and the resulting solution was allowed to warm to room temperature and stirred for another 4 hours to form 4-((4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-quinoline-3-carboxylic acid hydroxyamide (I').

DEFINITIONS - Preferred Definitions:
W, X = C;
T = N;
U = C optionally substituted by R1;
P = -N(-CH2-R5)-S(=O)2-Z;
Q = -C(O)NHOH;
A = phenyl or pyrazole (both optionally substituted by 1-3 R1).

L51 ANSWER 10 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-424086 [45] WPIX
CROSS REFERENCE: 1999-312431 [26]; 2001-656404 [75]; 2002-146947 [19]; 2003-456157 [43]

DOC. NO. CPI: C2001-128285
TITLE: New ortho-sulfonamido bicyclic **hydroxamic** acids, useful as antiarthritic agents having **matrix metalloproteinase** and **TACE inhibiting** action.
DERWENT CLASS: B02
INVENTOR(S): ALBRIGHT, J D; DU, X; GU, Y; LEVIN, J I; ZASK, A
PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 6228869	B1	20010508	(200145)*		31	A61K031-47

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6228869	B1 Provisional	US 1996-28505P	19961016
	CIP of	US 1997-944188	19971006
	CIP of	US 1998-55856	19980406
		US 1998-59554	19980414

PRIORITY APPLN. INFO: US 1996-28505P 19961016; US 1997-944188 19971006; US 1998-55856 19980406; US 1998-59554 19980414
INT. PATENT CLASSIF.:
MAIN: A61K031-47
SECONDARY: C07D215-38; C07D217-00
BASIC ABSTRACT:
US 6228869 B UPAB: 20030707
NOVELTY - Ortho-sulfonamido bicyclic **hydroxamic** acids (I) and their salts are new.
DETAILED DESCRIPTION - Ortho-sulfonamido bicyclic **hydroxamic** acids of formula (I) and their salts are new.
P, Q = group of formula (i) or (ii); provided that when P is (i) then Q is (ii) and vice versa;
W, X = C;
T, U = N or C; provided that when T is N then U is C, when T is C then U is N and when T or U is C, either may be optionally substituted;
W and X with the ring = phenyl optionally mono-, di- or tri-substituted with R1;
Z = phenyl, naphthyl, heteroaryl containing 5-6 ring atoms and 1-3 heteroatoms selected from N, O or S, optionally fused to phenyl, the phenyl, naphthyl, heteroaryl may be optionally mono-, di- or tri-substituted with R1;
R1 = H, halo, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, (CH2)nZ, OR2, CN, COR2, 1-4C perfluoroalkyl, CONR2R3, S(O)xR2, OPO(OR2)OR3, PO(OR3)R3, OC(O)NR2R3, COOR2, CONR2R3, SO2H, NR2R1, NR2COR3, NR3COOR3, SO2NR2R3, NO2, N(R2), SO2R3, NR2CONR2R2, NR3C(=NR3)NR2R2, SO2NHCOR1, CONHSO2R1, tetrazol-5-yl, SO2NHCN, SO2NHCONR2R1, or Z;
V = saturated or partially unsaturated heterocycloalkyl ring of 5-7 ring atoms with 1-3 heteroatoms selected from N, O, or S, optionally mono-, di- substituted with R2;
R2, R3 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C perfluoroalkyl, Z or V;
R4 = 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 1-4C

perfluoroalkyl, Z or V;
R5 = H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, Z or V;
n = 1-6; and
x = 0-2.

ACTIVITY - Antiarthritic; Cytostatic; Antiulcer; Vulnerary; antiinflammatory; Immunosuppressive; osteopathic; Anti-HIV; Antiarteriosclerotic; Cerebroprotective; antirheumatic; antibacterial; Hepatotrophic; Nephrotropic; Antidiabetic; Ophthalmological.

MECHANISM OF ACTION - **Matrix metalloproteinase** (**MMP**)-1, **MMP**-9, **MMP**-13 and **TNF-alpha converting** enzyme (**TACE**) **inhibitors.**

MMP inhibition was tested in-vivo on a rat (Sprague-Dawley, 150-200 g) or mouse (CD-1, 25-50 g) which were administered with the specific drugs, 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-**quinoline**-3-carboxylic acid hydroxyamide (Ia) showed an inhibition of 81% (50 mg/kg dose) p.o. versus **MMP**-13.

USE - (I) are useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection. They are also useful in treating or **inhibiting** pathological changes mediated by **MMPs** such as atherosclerosis, atherosclerotic osteopenias, inflammatory disease of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, age related muscular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D02; B06-D03; B07-H; B10-J02; B14-A02B1; B14-C03; B14-C09; B14-D03; B14-D07C; B14-E08; B14-E10C; B14-G02C; B14-H01; B14-J05B; B14-N01; B14-N03; B14-N06B; B14-N10; B14-N12; B14-S01; B14-S04

TECH UPTX: 20010813

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The 4-chloroquinoline carboxylic acid ester could be first reacted with R7-NH2 and the resulting 4-(R7-amino)quinoline carboxylic acid ester then reacted with the appropriate Z-SO2-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydro-chloride would then give the desired product.

ABEX UPTX: 20010813

WIDER DISCLOSURE - Ortho-sulfonamido bicyclic **hydroxamic** acids of formula (I), (II) and (III) and their salts are new.
Y' = C, N, O or S (provided that at least one of T, U, W, X and Y' is not C and further provided that no more than 2 of T, U, W and X are N); and W and X with the ring = phenyl or 5-6-membered heteroaryl ring containing 0-2 of N, O or S in addition to W and X.

SPECIFIC COMPOUNDS - 25 compounds are specifically claimed e.g. 4-((4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino)-8-methoxy-**quinoline**-3-carboxylic acid hydroxyamide of formula (Ia).

ADMINISTRATION - Projected oral daily dosages are 2-500 mg/kg, preferred oral daily dosages are 2-50 mg/kg and more preferred oral daily dosages are 5-25 mg/kg.

EXAMPLE - To a solution of 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-**trifluoromethylquinoline**-3-carboxylic acid (0.636 g) in dichloromethane (12.5 ml) was added dimethylformamide (0.05 ml) followed by 2M oxalyl chloride (1.26 ml) and stirred at room temperature for 1 hour. In a separate flask triethylamine (2.6 ml) was added to a 0degreesC mixture of hydroxylamine hydrochloride (350 mg) in tetrahydrofuran (14 ml) and water (3.5 ml). After stirring for 15 minutes at 0degreesC the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature and stirred for another 4 hours. Water was then added to the reaction flask and 4-(benzyl-(4-methoxy-benzenesulfonyl)-amino)-7-**trifluoromethylquinoline**-3-carboxylic acid hydroxyamide (0.488 g) was collected via filtration.

L51 ANSWER 11 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-564722 [52] WPIX
DOC. NO. CPI: C2000-168195
TITLE: New N-(carboxyalkyl)-N-(biarylsulfonyl)glycyl hydroxamic acids, useful for treating e.g. arthritis, cancer, ulcers, periodontal disease, bone resorption, autoimmune disorders and AIDS.
DERWENT CLASS: B05
INVENTOR(S): ROBINSON, R P
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 6107337	A	20000822 (200052)*			14	A61K031-35

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6107337	A	US 1998-130922	19980806

PRIORITY APPLN. INFO: US 1998-130922 19980806
INT. PATENT CLASSIF.:
MAIN: A61K031-35
SECONDARY: A61K031-216; A61K031-50; A61K031-5375
BASIC ABSTRACT:
US 6107337 A UPAB: 20001018
NOVELTY - N-(Carboxyalkyl)-N-(biarylsulfonyl)glycyl **hydroxamic** acids (I) and their salts are new
DETAILED DESCRIPTION - N-(Carboxyalkyl)-N-(biarylsulfonyl)glycyl **hydroxamic** acids of formula (I) and their salts are new:
Ar = 6-10C aryl-6-10C aryl;
n = 1-6;
X = hydroxy, 1-6C alkoxy, or NR1R2;
R1, R2 = H, 1-6C alkyl, piperidyl, 1-6C alkylpiperidyl, Y-piperidyl, Y-(1-6C alkylpiperidyl), 1-6C acylpiperidyl, Y, Y-(1-6C alkyl), 6-10C aryl 6-10C aryl, 6-10C aryl 6-10C aryl 1-6C alkyl, 3-6C alkyl, 3-6C cycloalkyl 1-6C alkyl, R5-(2-6C alkyl), R6-(1-6C alkyl), 1-5C alkyl (CH(R6) 1-6C alkyl), or CH(R7)COR8;

Y = 6-10C aryl or 2-9C heteroaryl;
provided that, when one of R1, R2 = CH(R7)COR8, the other is H, 1-6C alkyl, or benzyl;
R5 = hydroxy, or 1-6C alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy or acylamino, 6-10C arylthio, arylsulfinyl, or arylsulfonyl, amino, mono- or di- (1-6C alkyl)amino, piperazinyl, (1-6C acyl)piperazinyl, (1-6C alkyl)piperazinyl Y-(1-6C alkyl)piperazinyl, morpholinyl, thiomorpholinyl, piperidyl, or pyrrolidyl;
R6 = piperidyl, (1-6C alkyl)piperidyl, Y-piperidyl, or Y-(1-6C alkyl)piperidyl;
R7 = H, 1-6C alkyl, aminoalkyl, or hydroxyalkyl, Y-(1-6C alkyl), 1-6C alkylthio 1-6C alkyl, 6-10C arylthio 1-6C alkyl, 1-6C alkylsulfinyl 1-6C alkyl, 6-10C arylsulfinyl 1-6C alkyl, 1-6C alkylsulfonyl 1-6C alkyl, 6-10C arylsulfonyl 1-6C alkyl, mono- or di- (1-6C alkyl)amino 1-6C alkyl, R9R10NCO(1-6C alkyl), or R9OCO(1-6C alkyl);
R8 = OR11 or NR11R12;
R9, R10, R11, R12 = H, 1-6C alkyl, or Y-(1-6C alkyl); or
R1+R2 , R9+R10, R11+R12 = azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, piperazinyl, **tetrahydroquinolinyl**, **tetrahydroisoquinolinyl**, (1-6C acyl)piperazinyl, (1-6C alkyl)piperazinyl, Q-piperazinyl, or a bridged diazabicycloalkyl group of formula (a)-(e):
r = 1-3;
m = 1 or 2;
p = 0 or 1;
Q = H, 1-3C alkyl, or 1-6C acyl;
R3, R4 = H, 1-6C alkyl or hydroxyalkyl, CF3, CF3(1-6C alkyl), 1-6C alkyl-(CF2), 1-3C alkyl-(CF2)(1-3C alkyl), Y, Y-(1-6C alkyl), 6-10C aryl 6-10C aryl, 6-10C aryl 6-10C aryl 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl 1-6C alkyl, 1-6C acyloxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, piperazinyl 1-6C alkyl, 1-6C acylamino 1-6C alkyl, piperidyl, (1-6C alkyl)piperidyl, Y-(1-6C alkoxy) 1-6C alkyl, 1-6C alkylthio 1-6C alkyl, 6-10C arylthio 1-6C alkyl, 1-6C alkylsulfinyl 1-6C alkyl, 6-10C arylsulfinyl 1-6C alkyl, 1-6C alkylsulfonyl 1-6C alkyl, 6-10C arylsulfonyl 1-6C alkyl, 1-6C aminoalkyl, mono- or di- (1-6C alkyl)amino 1-6C alkyl, R13CO-(1-6C alkyl), or R14(1-6C alkyl);
R13 = OR20 or NR20R21;
R14 = 1-6C acylpiperazinyl, Y-piperazinyl, (1-6C alkyl)piperazinyl, Y-(1-6C alkyl)piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperidyl, (1-6C alkyl)piperidyl, Y-piperidyl, or (1-6C acyl)piperidyl; or
R3+R4, R20+R21 = 3-6C cycloalkyl, tetrahydropyranyl, tetrahydropyranyl, indanyl, tetrahydronaphthyl, or R15-(piperidyl); and
R15 = H, 1-6C acyl or alkyl or alkylsulfonyl, or Y-(1-6C alkyl) .
ACTIVITY - Cytostatic; osteopathic; antiarthritic; antirheumatic; vulnerary; vasotropic; antiarteriosclerotic; neuroprotective; ophthalmological; anti-HIV; antibacterial; immunosuppressive.
MECHANISM OF ACTION - (I) are **matrix metalloproteinase** (**MMP**) **inhibitors**, particularly of **MMP**-13, and **inhibitors** of **tumor necrosis** factor (**TNF**) production.
In **MMP inhibition** tests, 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)propionic acid, methyl ester (Ib) had IC50 against human **MMP**-1 (collagenase) of 80 nM and against **MMP**-13 of 10 nM; the corresponding IC50 values for the corresponding acid were 195 and 1.7 nM respectively.
USE - For treating **MMP** and **TNF** modulated disorders, including osteo- and rheumatoid arthritis, cancer including metastasis and invasion, tissue (e.g., corneal, gastric, and gastric) ulceration, abnormal wound healing, restenosis, periodontal disease,

epidermolysis bullosa, restenosis, bone resorption, loosening of artificial joint implants, osteoporosis, Paget's disease, atherosclerosis, multiple sclerosis, ocular angiogenesis leading to e.g., macular degeneration, HIV infection, AIDS, sepsis, and septic shock.
Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B10-A08; B14-C09; B14-D07C; B14-F02D; B14-F07; B14-G01B; B14-H01; B14-L06; B14-N01; B14-N03; B14-N06B; B14-N17; B14-S01; B14-S06

TECH UPTX: 20001018
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by successive arylsulfonylation and N-alkylation of glycine esters, followed by conversion of the ester group into hydroxamic acid.

ABEX UPTX: 20001018
SPECIFIC COMPOUNDS - 4 Compounds (I) are specifically claimed, e.g.: 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)propionic acid (Ia) and its methyl ester (Ib).

ADMINISTRATION - Administration is e.g. oral, topical or parenteral. Dosage is 0.1-25 (preferably 0.3-5) mg/kg/day.

EXAMPLE - 1-Aminocyclopentanecarboxylic acid was converted into 1-((4'-fluorobiphenyl-4-sulfonyl)-(2-methoxycarbonylethyl)amino)cyclopentanecarboxylic acid benzyl ester by standard acylation and alkylation procedures with appropriate protections, and the benzyl group removed by hydrogenation in 100% yield. The acid (10.1 g) in DMF (170 ml) was treated with (i-Pr)2NEt (4.3 ml) followed by BOP reagent (11.0 g) for 4 hours. More (i-Pr)2NEt (7.8 ml) and O-benzylhydroxylamine HCl (4.64 g) were added, and the mixture stirred at 60degreesC for 16 hours. Work-up was by evaporation and EtOAc/aqueous (1N HCl, water, NaHCO3, and brine) partitions, with purification by trituration with hexane/EtOAc/CH2Cl2 7:3:1 to give the benzyl protected product which was hydrogenated to give 3-((4'-fluorobiphenyl-4-sulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino)propionic acid, methyl ester (Ib).

L51 ANSWER 12 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-170753 [15] WPIX
DOC. NO. CPI: C2000-052983
TITLE: New substituted aryl hydroxamic acids used for treatment of fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia.
DERWENT CLASS: B05
INVENTOR(S): DECICCO, C P; WEXLER, R R; XUE, C
PATENT ASSIGNEE(S): (DUPO) DU PONT PHARM CO; (DUPO) DUPONT PHARM CO
COUNTRY COUNT: 45
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9958528	A1	19991118	(200015)*	EN	70	C07D405-12
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE						
W: AU BR CA CN CZ EE HU IL IN JP KR LT LV MX NO NZ PL RO SG SI SK UA VN ZA						
AU 9940747	A	19991129	(200018)			C07D405-12
EP 1077974	A1	20010228	(200113)	EN		C07D405-12
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV NL PT RO SE SI						
US 6268379	B1	20010731	(200146)			C07D217-00
JP 2002514644	W	20020521	(200236)		74	C07D401-12

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9958528	A1	WO 1999-US10358	19990512
AU 9940747	A	AU 1999-40747	19990512
EP 1077974	A1	EP 1999-924184	19990512
		WO 1999-US10358	19990512
US 6268379	B1 Provisional	US 1998-85393P	19980514
		US 1999-311168	19990513
JP 2002514644	W	WO 1999-US10358	19990512
		JP 2000-548332	19990512

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9940747	A Based on	WO 9958528
EP 1077974	A1 Based on	WO 9958528
JP 2002514644	W Based on	WO 9958528

PRIORITY APPLN. INFO: US 1998-85393P 19980514; US 1999-311168 19990513

INT. PATENT CLASSIF.:

MAIN: C07D217-00; C07D401-12; C07D405-12

SECONDARY: A61K031-35; A61K031-44; A61K031-4433; A61K031-445; A61K031-4545; A61K031-47; A61K031-4709; A61K031-4725; A61K031-506; A61P001-02; A61P007-02; A61P007-04; A61P009-00; A61P009-02; A61P009-04; A61P009-10; A61P011-00; A61P011-06; A61P019-02; A61P025-00; A61P027-02; A61P029-00; A61P031-00; A61P031-04; A61P031-06; A61P031-08; A61P031-18; A61P033-06; A61P035-00; A61P035-04; A61P037-06; A61P043-00; C07D213-02; C07D401-14; C07D471-04

BASIC ABSTRACT:

WO 9958528 A UPAB: 20000323

NOVELTY - Substituted **hydroxamic** acid compounds (I) and (II) are new.

DETAILED DESCRIPTION - Substituted **hydroxamic** acid compounds of formulae (I) and (II) are new.

ring A = 5-8 membered cyclic system containing 0-2 heteroatoms chosen from O, NH, S, SO or SO2 and substituted with 0-3 Ra;

Ra = O, CH3, CH2CH3, CF3, Cl, F, OH, OCH3 or OCF3;

Rb = F or CH3;

X = CH2C(O), CH2C(O)O, CH2C(O)NH, CH2S(O), CH2S(O)2, CH2S(O)NH or CH2S(O)2NH;

Y = OCH2, CH2O, OCH(CH3), CH(CH3)O, OC(CH3)2, C(CH3)2O, OCF2, CF2O, S(O)pCH2, CH2S(O)p, NHCH2 or CH2NH;

Z = CH or N;

R1 = H, F, Cl, Br, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3;

R2 = F, Cl, Br, I, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3;

R3 = F, Cl, Br, I, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3;

R4 = H;

p = 0-2;

Y' = CH2, O or NH.

When Z = N, then R2 and R3 are = F, Br or I. Alternately, R3 and R4 form 5-6 membered aromatic ring containing 0-2 heteroatoms chosen from O,

S, NH, and N, and the aromatic ring is substituted with 0-2 Rc.
Rc = H, F, Cl, Br, I, NO2, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3.
ACTIVITY - Anti-inflammatory; Antiarthritic.
MECHANISM OF ACTION - **Inhibits matrix metalloproteinase (MMP)** and **tumor necrosis** factor (**TNF**).
USE - Used for treatment of fever, cardiovascular diseases, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, solid tumor growth and tumor invasion by secondary metastases, or neovascular glaucoma, rheumatoid, arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, multiple sclerosis, neurodegenerative, diseases, psoriasis, autoimmune disease, Crohn's disease, inflammatory bowel disease, or HIV infection (all claimed).
Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B14-C09; B14-D07C; B14-E10; B14-G01B; B14-G02D; B14-J01B3; B14-N03; B14-N06B; B14-N17C; B14-S01

TECH UPTX: 20000323
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (Disclosed) The lactone derivatives of piperidine, 3,4,5,6-tetrahydro-2(1H)-pyrimidinone and tetrahydropyran are converted into a phenylether intermediate, which is then converted into hydroxamic acid by coupling with hydroxylamine hydrochloride using BOP. Oxidation using oxone produces the desired sulfone.

ABEX UPTX: 20000323
SPECIFIC COMPOUNDS - The compound (I) is chosen from 19 claimed compounds, one of them is tetrahydro-N-hydroxy-4-(((4-(4-**quinolinylmethoxy**) phenyl) sulfonyl)methyl)-2H-pyran-4-carboxamide, which is represented by formula (IV).

ADMINISTRATION - Oral; Topical; Intranasal, Transdermal; Daily oral dosage ranges between 0.001-1000 mg/kg body weight, most preferably 1-20 mg/kg/day.

EXAMPLE - To a cooled solution of 4-mercaptophenol (1.33g, 10.6 mmol) in THF (30 mL) was added NaH (0.98g, 24.6 mmol). Mixture was allowed to warm to room temperature, and added with a solution of 2,7-dioxaspiro(3,5)nonane-1-one (1.0 g, 7 mmol) in THF (5 mL). The mixture was stirred, quenched with 1 N HCl, and extracted with ethyl acetate followed by washing the organic layers with carboxylic acid. The solution of the acid (1a) (700 mg, 2.6 mmol) and 4-dimethylaminopyridine (63 mg, 0.5 mmol) in methylene chloride (5 mL) and methanol (1 mL) was added with 1,3-dicyclohexylcarbodiimide (640 mg, 3.1 mmol). The mixture was filtered, concentrated and chromatographically eluted to obtain methyl ester. The methyl ester (300 mg), 2,6-dimethyl-4-picolyl chloride (213 mg), cesium carbonate (1.03 g), and tetrabutylammonium iodide (392 mg) in DMSO (3mL) were heated at 50 degreesC. Ethyl acetate was added and the solution was washed, dried, concentrated and chromatographed on a reversed HPLC to give the phenylether as a TFA salt. The phenylether (200 mg) in methanol (5 mL) and 1 N LiOH (4mL) was refluxed for 5 hours. The solution was acidified with 1 N HCl and concentrated. The crude acid (0.388 mmol), hydroxylamine hydrochloride (139 mg, 2 mmol) and diisopropylethylamine (0.7 mL, 4 mmol) in DMF (3 mL) were cooled in an ice bath and BOP (220 mg, 0.5 mmol) was added. The mixture was stirred at room temperature for 2 hours and concentrated. Purification on HPLC gave the **hydroxamic** acid. A solution of cooled the phenylether (95 mg) in methanol (3 mL) cooled in an ice bath was added a solution of oxone (0.28 g) in water (1 mL). The

mixture was stirred at room temperature for 4 hours and insoluble material was filtered off and the solution was concentrated. On purification using reversed high performance liquid chromatography (HPLC), (11 mg) of 4-(((4-(2,6-dimethyl-4-pyridinyl)methoxy)phenyl)sulfonyl)methyl)tetrahydro-N-hydroxy-2H-pyran-4-carboxamide mono(trifluoroacetate) was obtained.

DEFINITIONS - Preferred Definitions:
X = CH2, C(O), C(O)O, C(O)NH, S(O), S(O)2, S(O)NH or S(O)2NH;
Y = (CH2)2, OCH2, CH2O, NHCH2 or CH2NH;
Y' = CH2, O, S or NH;
R3 and R4 = (optionally) is one of 27 claimed aromatic rings, e.g. formula (III);
R2a = H, F, Cl, Br, I, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3;
Rc = H, F, Cl, Br, I, NO2, CH3, CH2CH3, CH(CH3)2, OCH3, OCH2CH3, OCH(CH3)2, CF3 or OCF3.

L51 ANSWER 13 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-312004 [27] WPIX
DOC. NO. CPI: C1998-096182
TITLE: New ortho-sulphonamide hetero-aryl **hydroxamic** acid derivatives - are **matrix metallo -proteinase** and **tumour necrosis alpha converting** enzyme **inhibitors** used for treating arthritis and tumour growth, etc..
DERWENT CLASS: B05 D21
INVENTOR(S): ALBRIGHT, J D; DUI, X; GU, Y; LEVIN, J I; ZASK, A; DU, X
PATENT ASSIGNEE(S): (AMCY) AMERICAN CYANAMID CO
COUNTRY COUNT: 77
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9816514	A1	19980423	(199827)*	EN	57	C07D215-54
RW: AT BE CH DE DK ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW						
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW						
AU 9749806	A	19980511	(199837)			C07D215-54
ZA 9709235	A	19990630	(199931)		57	C07D000-00
AU 743901	B	20020207	(200224)			C07D215-54

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9816514	A1	WO 1997-US18281	19971008
AU 9749806	A	AU 1997-49806	19971008
ZA 9709235	A	ZA 1997-9235	19971015
AU 743901	B	AU 1997-49806	19971008

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9749806	A	Based on	WO 9816514
AU 743901	B	Previous Publ.	AU 9749806

Based on WO 9816514

PRIORITY APPLN. INFO: US 1996-732004 19961016
INT. PATENT CLASSIF.:
MAIN: C07D000-00; C07D215-54
SECONDARY: A61K031-47; C07D401-12; C07D409-12; C07D409-14; C07D471-04; C07F000-00

BASIC ABSTRACT:

WO 9816514 A UPAB: 19980709

Ortho-sulphonamide bicyclic heteroaryl **hydroxamic** acid derivatives of formula (I) and their salts and optical isomers or diastereoisomers are new. A = 5-6 membered heteroaryl containing 1-2 heteroatoms comprising N, O and/or S (substituted by R1 and R2 on adjacent atoms); CR1CR2 = a fused Ph or 5-6 membered heteroaryl containing 1-3 heteroatoms comprising N, O and/or S (either ring optionally substituted by R4); **hydroxamic** acid and sulphonamido groups are bonded to adjacent C atoms of heteroaryl ring of A; Z = aryl, heteroaryl or heteroaryl fused to Ph; aryl = Ph or naphthyl (optionally substituted by R1-R4); heteroaryl = 5-6 membered heteroaromatic ring containing 1-3 heteroatoms comprising N, O and/or S (optionally substituted by R1-R4), provided that when heteroaryl is fused to Ph, at least 1 ring is optionally substituted by R1-R4; R1-R4 = H, COR5, F, Br, Cl, I, C(O)NR5OR6, CN, OR5, 1-4C perfluoroalkyl, SOxR5, OPO(OR5)(OR6), PO(OR6)R5, OC(O)NR5R6, CO2R5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5COOR6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, NR5C(=NR6)NR5R6, cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', tetrazol-5-yl, SO2NHCN, SO2NHCONR5R6, 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl or 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)); Q = COR5, CN, 2-6C alkenyl, 2-6C alkynyl, OR5, 1-4C perfluoroalkyl, SOxR5, OC(O)NR5R6, CO2R5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5CO2R6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', PO(OR5)OR6, PO(OR6)R5, tetrazol-5-yl, C(O)NR5OR6, NR5C(=NR6)NR5R6, SO2NHCONR5R6 or SO2NHCN; x = 0-2; cychet = 3-6 membered cycloheteroalkyl (containing 1-3 heteroatoms comprising O, N and/or S and optionally having 1-2 double bonds and optionally substituted by 1-3 R5); R5, R6 = H, aryl, heteroaryl, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, 1-4C perfluoroalkyl or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by OH, COR8, CN, C(O)NR8OR9, 2-6C alkenyl, 2-6C alkynyl, OR8, 1-4C perfluoroalkyl, SOxR8, OPO(OR8)OR9, PO(OR8)R9, OC(O)NR8R9, CO2R8, CONR8R9, SO3H, NR8R9, NHCOR8R9, NR8CO2R9, SO2NR8R9, NO2, NR8SO2R9, NR8CONR8R9, 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, aryl, heteroaryl, SO2NHCOR8', CONHSO2R8', tetrazol-5-yl, NR8C(=NR9)NR8R9, SO2NHCONR8R9 or SO2NHCN); R5' = a group R5 excluding H; R7 = (a) H or 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by OH, COR5, CN, 2-6C alkenyl, 2-6C alkynyl, OR5, 1-4C perfluoroalkyl, SOxR5, OPO(OR5)OR6, PO(OR5)R6, OC(O)NR5R6, COOR5, CONR5R6, SO3H, NR5R6, NR5COR6, NR5COOR6, SO2NR5R6, NO2, N(R5)SO2R6, NR5CONR5R6, 3-6C cycloalkyl, cychet, aryl, heteroaryl, SO2NHCOR5', CONHSO2R5', tetrazol-5-yl, NR5C(=NR6)NR5R6, CONR5OR6, SO2NHCONR5R6 or SO2NHCN; (b) Ph or naphthyl (optionally substituted by R1-R4) or 5-6 membered heteroaryl containing 1-3 heteroatoms comprising N, O and/or S and optionally substituted by R1-R4 or (c) 3-6C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)) or cychet or R7CH2NA = a non-aromatic 7-12 membered heterocycle optionally containing an additional heteroatom selected from O, S and N and optionally fused to another benzene ring; R8, R9 = H, aryl, heteroaryl, 3-7C cycloalkyl (optionally having 1-2 double bonds (each optionally substituted by Q)), cychet, 1-4C perfluoroalkyl, 1-6C alkyl, 2-6C alkenyl

or 2-6C alkynyl (all optionally substituted by OH, alkoxy, aryloxy, 1-4C perfluoroalkyl, amino, mono- or di-(1-6C alkyl)amino, carboxylic acid, carboalkoxy or carboaryloxy), NO2, CN, carboxamido primary, mono- or di-(1-6C alkyl)carbamoyl; R8' = a group R8 excluding H. N.B. Some of the groups are cyclical.

52 Compounds are specifically claimed eg: 4-(benzyl-(4-methoxy-benzenesulphonyl)amino)-7-trifluoromethyl-**quinoline**-3-carboxylic acid hydroxyamide.

USE - (I) are **matrix metalloproteinase** (**MMP**) and **tumour necrosis** factor **alpha converting** enzyme **inhibitors** used to **inhibit** e.g. gelatinases, stromelysins and collagenases. (I) are useful for treating atherosclerosis, atherosclerotic plaque formation, **reduction** of coronary thrombosis from atherosclerotic plaque rupture, **MMP** mediated osteopenias, inflammatory of the central nervous system, skin ageing, angiogenesis, tumour metastasis, tumour growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of foetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, ketatoconus, Sjogren's syndrome, myopia, ocular tumours, ocular angiogenesis and neovascularisation, corneal graft rejection, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure and HIV infection.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D02; B07-D04C; B07-D08; B14-A02B1; B14-C03; B14-C09; B14-D07C; B14-E10; B14-F01B; B14-F02; B14-G02D; B14-H01; B14-J01; B14-N03; B14-N10; B14-N12; B14-N17B; D08-A05; D08-B09A

L51 ANSWER 14 OF 85 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-425356 [42] WPIX
DOC. NO. CPI: C1996-134034
TITLE: New aryl-sulphonyl-amino **hydroxamic** acid derivs. - are **matrix metallo-proteinase inhibitors** and **inhibitors** of production of **tumour necrosis** factor, used for treating arthritis and cancer, etc..
DERWENT CLASS: B03 B05 D21
INVENTOR(S): RIZZI, J P; ROBINSON, R P
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER CORP
COUNTRY COUNT: 74
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9627583	A1	19960912	(199642)*	EN	70	C07C311-29
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG						
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN						
AU 9650293	A	19960923	(199702)			C07C311-29

ZA 9601876	A	19971126	(199802)		56	C07C000-00
NO 9704103	A	19971105	(199804)			C07C311-29
EP 813520	A1	19971229	(199805)	EN		C07C311-29
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE						
FI 9703613	A	19971105	(199806)			C07C000-00
BR 9607362	A	19971230	(199807)			C07C311-29
NZ 303860	A	19980826	(199840)			C07C311-29
HU 9800462	A2	19980728	(199842)			C07C311-29
CZ 9702782	A3	19981111	(199851)			C07C311-29
MX 9706850	A1	19971101	(199902)			C07C311-29
US 5863949	A	19990126	(199911)			A61K031-185
JP 11501910	W	19990216	(199917)		71	C07C311-29
TW 346488	A	19981201	(199919)			C07D265-30
KR 98702820	A	19980805	(199932)			C07C311-29
AU 707510	B	19990715	(199939)			C07C311-29
US 5994351	A	19991130	(200003)			A61K031-495
RU 2145597	C1	20000220	(200048)			C07C311-29
US 6147074	A	20001114	(200060)			A61K031-192
KR 269046	B1	20001016	(200138)			C07C311-29
EP 813520	B1	20011219	(200206)	EN		C07C311-29
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE						
CN 1316419	A	20011010	(200207)			C07C311-29
DE 69618179	E	20020131	(200216)			C07C311-29
US 6380219	B1	20020430	(200235)			A61K031-4468
CN 1181066	A	19980506	(200236)			C07C311-29
ES 2169794	T3	20020716	(200256)			C07C311-29
IL 117343	A	20020814	(200272)			C07C311-19
NO 313752	B1	20021125	(200302)			C07C311-29
CZ 291106	B6	20021211	(200309)			C07C311-29
MX 208185	B	20020605	(200366)			A61K031-18
CA 2214720	C	20040127	(200412)	EN		A61K031-535
CN 1122662	C	20031001	(200553)			C07C311-29

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9627583	A1	WO 1996-US2679	19960307
AU 9650293	A	AU 1996-50293	19960307
ZA 9601876	A	ZA 1996-1876	19960307
NO 9704103	A	WO 1996-US2679	19960307
		NO 1997-4103	19970905
EP 813520	A1	EP 1996-907134	19960307
		WO 1996-US2679	19960307
FI 9703613	A	WO 1996-US2679	19960307
		FI 1997-3613	19970905
BR 9607362	A	BR 1996-7362	19960307
		WO 1996-US2679	19960307
NZ 303860	A	NZ 1996-303860	19960307
		WO 1996-US2679	19960307
HU 9800462	A2	WO 1996-US2679	19960307
		HU 1998-462	19960307
CZ 9702782	A3	WO 1996-US2679	19960307
		CZ 1997-2782	19960307
MX 9706850	A1	MX 1997-6850	19970908
US 5863949	A	WO 1996-US2679	19960307
		US 1997-894873	19970804
JP 11501910	W	JP 1996-526918	19960307
		WO 1996-US2679	19960307
TW 346488	A	TW 1996-104697	19960419

KR 98702820	A		WO 1996-US2679	19960307
			KR 1997-706227	19970906
AU 707510	B		AU 1996-50293	19960307
US 5994351	A	Div ex	WO 1996-US2679	19960307
		Div ex	US 1997-894873	19970804
			US 1998-122920	19980727
RU 2145597	C1		WO 1996-US2679	19960307
			RU 1997-116727	19960307
US 6147074	A	Div ex	WO 1996-US2679	19960307
		Div ex	US 1997-894873	19970804
		Div ex	US 1998-122920	19980727
			US 1999-406522	19990928
KR 269046	B1		WO 1996-US2679	19960307
			KR 1997-706227	19970906
EP 813520	B1		EP 1996-907134	19960307
			WO 1996-US2679	19960307
CN 1316419	A		CN 2001-111743	20010323
DE 69618179	E		DE 1996-618179	19960307
			EP 1996-907134	19960307
			WO 1996-US2679	19960307
US 6380219	B1	Div ex	US 1997-894873	19970804
		Div ex	US 1998-122920	19980727
		Div ex	US 1999-406522	19990928
			US 2000-635186	20000808
CN 1181066	A		CN 1996-193213	19960307
ES 2169794	T3		EP 1996-907134	19960307
IL 117343	A		IL 1996-117343	19960304
NO 313752	B1		WO 1996-US2679	19960307
			NO 1997-4103	19970905
CZ 291106	B6		WO 1996-US2679	19960307
			CZ 1997-2782	19960307
MX 208185	B		WO 1996-US2679	19960307
			MX 1997-6850	19970908
CA 2214720	C		CA 1996-2214720	19960307
			WO 1996-US2679	19960307
CN 1122662	C		CN 1996-193213	19960307

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9650293	A	Based on	WO 9627583
EP 813520	A1	Based on	WO 9627583
BR 9607362	A	Based on	WO 9627583
NZ 303860	A	Based on	WO 9627583
HU 9800462	A2	Based on	WO 9627583
CZ 9702782	A3	Based on	WO 9627583
US 5863949	A	Based on	WO 9627583
JP 11501910	W	Based on	WO 9627583
KR 98702820	A	Based on	WO 9627583
AU 707510	B	Previous Publ.	AU 9650293
		Based on	WO 9627583
US 5994351	A	Div ex	US 5863949
RU 2145597	C1	Based on	WO 9627583
US 6147074	A	Div ex	US 5994351
EP 813520	B1	Based on	WO 9627583
DE 69618179	E	Based on	EP 813520
		Based on	WO 9627583
US 6380219	B1	Div ex	US 5863949
		Div ex	US 5994351

		Div ex	US 6147074
ES 2169794	T3	Based on	EP 813520
NO 313752	B1	Previous Publ.	NO 9704103
CZ 291106	B6	Previous Publ.	CZ 9702782
		Based on	WO 9627583
CA 2214720	C	Based on	WO 9627583

PRIORITY APPLN. INFO: US 1995-401049 19950308; US
1997-894873 19970804; US
1998-122920 19980727; US
1999-406522 19990928; US
2000-635186 20000808
REFERENCE PATENTS: EP 606046; WO 9005719
INT. PATENT CLASSIF.:
MAIN: A61K031-18; A61K031-185; A61K031-192; A61K031-4468; A61K031-495; A61K031-535; C07C000-00; C07C311-19; C07C311-29; C07D265-30; C07D295-185
SECONDARY: A61K031-195; A61K031-215; A61K031-335; A61K031-38; A61K031-395; A61K031-40; A61K031-44; A61K031-445; A61K031-47; A61K031-5375; A61K031-54; A61P001-04; A61P019-02; A61P029-00; A61P031-02; A61P031-18; A61P035-00; A61P037-00; A61P043-00; C07C303-40; C07C311-18; C07C317-26; C07C323-23; C07C323-50; C07D207-12; C07D207-335; C07D209-08; C07D209-44; C07D211-06; C07D211-26; C07D211-56; C07D211-60; C07D211-66; C07D213-40; C07D213-56; C07D213-75; C07D215-08; C07D217-06; C07D241-04; C07D241-08; C07D295-12; C07D295-15; C07D295-18; C07D295-19; C07D295-192; C07D309-08; C07D309-14; C07D335-02; C07D401-02; C07D403-02; C07D405-02; C07D409-02; C07D413-02; C07D413-12; C07D417-02; C07D471-08; C07D473-00; C07D487-08

BASIC ABSTRACT:

WO 9627583 A UPAB: 19981021

Arylsulphonylamino **hydroxamic** acid derivs. of formula (I) and their salts are new. n = 1-6; X = OH, 1-6 C alkoxy or NR1R2; R1, R2 = e.g. H, 1-6 C alkyl, piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 5-9 C heteroaryl-piperidyl, 6-10 C aryl, 1-6 C alkyl-piperidyl, R5(2-6 C alkyl), 1-5 C alkyl (CHR5)-1-6 C alkyl, R-6(1-6 C alkyl), 1-56 C alkyl (CHR6)-1-6 C alkyl or CH(R7)COR8, etc.; R5 = e.g. OH, 1-6 C acyloxy, 1-6 C alkoxy, piperazino, 1-6 C acylamino, 1-6 C alkylthio, 6-10 C arylthio, 1-6 C alkyl-sulphinyl, etc.; R6 = piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 6-10C aryl-1-6 C alkyl-piperidyl, 5-9 C heteroaryl-piperidyl or 5-9 C heteroaryl-1-6 C alkyl-piperidyl; R7 = e.g. H, 1-6 C alkyl 6-10 C aryl-1-6 C alkyl, 5-9 C heteroaryl-1-6 C alkyl, 1-6 C alkylthio-1-6 C alkyl, 6-10 C arylthio-1-6 C alkyl, 1-6 C alkylsulphinyl-1-6 C alkyl, 6-10 C arylsulphinyl-1-6 C alkyl, or 1-6 C alkyl-sulphonyl-1-6 C alkyl, R9R10NCO-1-6 C alkyl or R9OCO-1-6 C alkyl, etc.; R8 = R11O or R11R12N; R9-R12 = H, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl or 5-9 C heteroaryl-1-6 C alkyl; or R1, R2, or R9 and R10, or R11 and R12 may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, **tetrahydroquinolinyl**, **tetrahydroisoquinolinyl**, 1-6 C acyl-piperazinyl, 1-6 C alkyl-piperazinyl, 6-10 C aryl-piperazinyl, 5-9 C heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from (a)-(e); r = 1-3; m = 1-2; p = 0-1; Q = H, 1-3 C alkyl or 1-6 C acyl; R3, R4 = e.g. H, 1-6 C alkyl, CF3, trifluoromethyl-1-6 C alkyl, 1-6 C alkyl (difluoromethylene), 1-3 C alkyl(difluoromethylene)- 1-3 C alkyl, 6-10 C aryl, 5-9 C heteroaryl, 6-10 C aryl-1-6 C alkyl, 1-6 C alkylsulphonyl-1-6 C alkyl, 6-10 C arylsulphonyl-1-6 C alkyl, amino-1-6 C alkyl, 1-6 C

alkylamino-1-6 C alkyl, (1-6 C alkylamino)2-1-6 C alkyl, R13CO -1-6 C alkyl or R14-1-6 C alkyl, etc.; R13 = R20O or R20R21N; R20, R21 = H, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl or 5-9 C heteroaryl-1-6 C alkyl; R14 = 1-6 C acyl-piperazino, 6-10 C aryl-piperazino, 5-9 C heteroaryl-piperazino, 1-6 C alkyl-piperazino, 6-10 C aryl-1-6 C alkyl-piperazino, 5-9 C heteroaryl- 1-6 C alkyl-piperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, 1-6 C alkyl-piperidyl, 6-10 C aryl-piperidyl, 5-9 C heteroaryl-piperidyl, 6-10 C aryl-1-6 C alkyl-piperidyl, 5-9 C heteroaryl-1-6 C alkylpiperidyl or 1-6 C acyl-piperidyl; or R3 and R4, or R20 and R21 may be taken together to form a 3-6 C cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a gp. of formula (f): R15 = H, 1-6 C acyl, 1-6 C alkyl, 6-10 C aryl-1-6 C alkyl, 5-9 C heteroaryl-1-6 C alkyl or 1-6 C alkylsulphonyl; Ar = 6-10 C aryl, 5-9 C heteroaryl, 1-6 C alkyl-6-10 C aryl, 1-6 C alkoxy-6-10 C aryl, (1-6 C alkoxy)2- 6-10 C aryl, 6-10 C aryloxy-6-10 C aryl, 5-9 C heteroaryloxy-6-10 C aryl, 1-6 C alkyl-5-9 C heteroaryl, 1-6 C alkoxy-5-9 C heteroaryl, (1-6 C alkoxy)2-5-9 C heteroaryl, 6-10 C aryloxy-5-9 C heteroaryl or 5-9 C heteroaryloxy-5-9 C heteroaryl; with the proviso that when either R1 or R2 is CH(R7) COR8, the other of R1 and R2 is H, 1-6 C alkyl or benzyl.

USE - (I) can be used to **inhibit matrix metalloproteinases(MMPs)** or to **inhibit** the production of **tumour necrosis** factor (**TNF**) in a mammal (claimed). (I) can be used to treat arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterised by **MMP** activity (claimed). (I) can also be used to treat AIDS, sepsis, septic shock and other diseases involving the production of **TNF** (claimed). (I) can be used in doses of e.g. 0.1-25, pref.0.3-5 mg/kg/day by e.g. oral, parenteral or topical routes.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B10-A08; B14-A02B1; B14-C09; B14-D07C; B14-F01E; B14-H01; B14-L06; B14-N06; B14-S06; D08-A05

=> d ibib ed ab hitind 15-
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 71 ANSWERS - CONTINUE? Y/(N):y

L51 ANSWER 15 OF 85 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003601428 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14684295
TITLE: **Tetrahydroisoquinoline** based sulfonamide **hydroxamates** as potent **matrix metalloproteinase** inhibitors.
AUTHOR: Ma Dawei; Wu Wengen; Yang Guoxin; Li Jingya; Li Jia; Ye Qizhuang
CORPORATE SOURCE: State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China.. madw@mail.sioc.ac.cn
SOURCE: Bioorganic & medicinal chemistry letters, (2004 Jan 5) 14 (1) 47-50.
Journal code: 9107377. ISSN: 0960-894X.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20031220
Last Updated on STN: 20040828
Entered Medline: 20040827

ED Entered STN: 20031220
Last Updated on STN: 20040828
Entered Medline: 20040827

AB The synthesis and **MMP** inhibitory activity of a series of **tetrahydroisoquinoline** based sulfonamide **hydroxamates** are described. In nine **MMPs** tested, most of the compounds display potent inhibition activity except for **MMP**-7. Some subtle isozyme selectivity is observed by varying the substituents at the 6- and 7-positions and aromatic ring of arylsulfonyl groups.

CT *Enzyme Inhibitors: CH, chemistry
Enzyme Inhibitors: PD, pharmacology
*Hydroxamic Acids: CH, chemistry
Hydroxamic Acids: PD, pharmacology
*Matrix Metalloproteinases: AI, antagonists & inhibitors
Matrix Metalloproteinases: ME, metabolism
Research Support, Non-U.S. Gov't
*Sulfonamides: CH, chemistry
Sulfonamides: PD, pharmacology
*Tetrahydroisoquinolines: CH, chemistry
Tetrahydroisoquinolines: PD, pharmacology

CN 0 (Enzyme Inhibitors); 0 (Hydroxamic Acids); 0 (Sulfonamides); 0 (Tetrahydroisoquinolines); EC 3.4.24.- (Matrix Metalloproteinases)

L51 ANSWER 16 OF 85 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002455012 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12213468
TITLE: Tetrahydroisoquinoline-3-carboxylate based matrix-metalloproteinase inhibitors: design, synthesis and structure-activity relationship.
AUTHOR: Matter Hans; Schudok Manfred; Schwab Wilfried; Thorwart Werner; Barbier Denis; Billen Gunter; Haase Burkhard; Neises Bernhard; Weithmann Klaus; Wollmann Theo
CORPORATE SOURCE: Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany.. hans.matter@aventis.com
SOURCE: Bioorganic & medicinal chemistry, (2002 Nov) 10 (11) 3529-44.
Journal code: 9413298. ISSN: 0968-0896.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20030305
Entered Medline: 20030304

ED Entered STN: 20020906
Last Updated on STN: 20030305
Entered Medline: 20030304

AB The design, synthesis and structure-activity relationship (SAR) of a series of nonpeptidic 2-arylsulfonyl-1,2,3,4-tetrahydro-**isoquinoline**-3-carboxylates and-**hydroxamates** as inhibitors of the **matrix metalloproteinase** human

neutrophil collagenase (**MMP**-8) is described here. Based on available X-ray structures of **MMP**-8/inhibitor complexes, our structure-based design strategy was directed to complement major protein-ligand interaction regions mainly in the S1' hydrophobic specificity pocket close to the catalytic zinc ion. Here, the rigid 1,2,3,4-**tetrahydroisoquinoline** scaffold (Tic) provides ideal geometry to combine **hydroxamates** and carboxylates as typical zinc complexing functionalities, with a broad variety of S1' directed mono- and biaryl substituents consisting of aromatic rings perfectly accommodated within this more hydrophobic region of the **MMP**-8 inhibitor binding site. The effect of different S1' directed substituents, zinc-complexing groups, chirality and variations of the tetrahydroisoquinoline ring-system is investigated by systematic studies. X-ray structure analyses in combination with 3D-QSAR studies provided an additional understanding of key determinants for **MMP**-8 affinity in this series. The hypothetical binding mode for a typical molecule as basis for our inhibitor design was found in good agreement with a 1.7 A X-ray structure of this candidate in complex with the catalytic domain of human **MMP**-8. After analysis of all systematic variations, 3D-QSAR and X-ray structure analysis, novel S1' directed substituents were designed and synthesized and biologically evaluated. This finally results in inhibitors, which do not only show high biological affinity for **MMP**-8, but also exhibit good oral bioavailability in several animal species.

CT Check Tags: In Vitro
Animals
Biological Availability
Computational Biology
Crystallography, X-Ray
Drug Design
Gelatinase B: AI, antagonists & inhibitors
Humans
Indicators and Reagents
*Isoquinolines: CS, chemical synthesis
*Isoquinolines: PD, pharmacology
*Matrix Metalloproteinases: AI, antagonists & inhibitors
Models, Molecular
Molecular Conformation
Neutrophils: DE, drug effects
Neutrophils: EN, enzymology
*Protease Inhibitors: CS, chemical synthesis
Protease Inhibitors: PK, pharmacokinetics
*Protease Inhibitors: PD, pharmacology
Quantitative Structure-Activity Relationship
Rabbits
*Tetrahydroisoquinolines

RN 41034-52-0 (1,2,3,4-tetrahydroisoquinoline carboxylic acid)
CN 0 (Indicators and Reagents); 0 (Isoquinolines); 0 (Protease Inhibitors); 0 (Tetrahydroisoquinolines); EC 3.4.24.- (Matrix Metalloproteinases); EC 3.4.24.35 (Gelatinase B)

L51 ANSWER 17 OF 85 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000048220 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10579815
TITLE: Affinity and selectivity of matrix metalloproteinase inhibitors: a chemometrical study from the perspective of ligands and proteins.
AUTHOR: Matter H; Schwab W
CORPORATE SOURCE: Hoechst Marion Roussel, Chemical Research, D-65926 Frankfurt am Main, Germany.. hans.matter@hmrag.com

SOURCE: Journal of medicinal chemistry, (1999 Nov 4) 42 (22) 4506-23.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991217

ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991217

AB A novel strategy to understand affinity and selectivity for enzyme inhibitors using information from ligands and target protein 3D structures is described. It was applied to 2-arylsulfonyl-1,2,3, 4-tetrahydro-**isoquinoline**-3-carboxylates and -**hydroxamates** as inhibitors of the **matrix metalloproteinases** **MMP**-3 (stromelysin-1) and **MMP**-8 (human neutrophil collagenase). As the first step, consistent and predictive 3D-QSAR models were derived using CoMFA, CoMSIA, and GRID/Golpe approaches, leading to the identification of binding regions where steric, electronic, or hydrophobic effects are important for affinity. These models were validated using multiple analyses using two or five randomly chosen cross-validation groups and randomizations of biological activities. Second, 3D-QSAR models were derived based on the affinity ratio IC(50)(**MMP**-8)/IC(50)(**MMP**-3), allowing the identification of key ligand determinants for selectivity toward one of both enzymes. In addition to this ligands' view, the third step encompasses a chemometrical approach based on principal component analysis (PCA) of multivariate GRID descriptors to uncover the major differences between both protein binding sites with respect to their GRID probe interaction pattern. The resulting information, based on the accurate knowledge of the target protein 3D structures, led to a consistent picture in good agreement with experimentally observed differences in selectivity toward **MMP**-8 or **MMP**-3. The interpretation of all three classes of statistical models leads to detailed SAR information for **MMP** inhibitors, which is in agreement with available data for binding site topologies, ligand affinities, and selectivities. Thus the combined chemical analyses provide guidelines and accurate activity predictions for designing novel, selective **MMP** inhibitors.

CT Carboxylic Acids: CH, chemistry
Hydroxamic Acids: CH, chemistry
Isoquinolines: CH, chemistry
Ligands
Models, Molecular
Molecular Structure
Neutrophil Collagenase: AI, antagonists & inhibitors
*Neutrophil Collagenase: CH, chemistry
*Protease Inhibitors: CH, chemistry
Protein Binding
Protein Conformation
Stromelysin 1: AI, antagonists & inhibitors
*Stromelysin 1: CH, chemistry
Structure-Activity Relationship

CN 0 (Carboxylic Acids); 0 (Hydroxamic Acids); 0 (Isoquinolines); 0 (Ligands); 0 (Protease Inhibitors); EC 3.4.24.17 (Stromelysin 1); EC 3.4.24.34 (Neutrophil Collagenase)

L51 ANSWER 18 OF 85 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999284661 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10354399
TITLE: Quantitative structure-activity relationship of human neutrophil collagenase (MMP-8) inhibitors using comparative molecular field analysis and X-ray structure analysis.
AUTHOR: Matter H; Schwab W; Barbier D; Billen G; Haase B; Neises B; Schudok M; Thorwart W; Schreuder H; Brachvogel V; Lonze P; Weithmann K U
CORPORATE SOURCE: Chemical Research & Core Research Functions, Hoechst Marion Roussel, D-65926 Frankfurt am Main, Germany.. hans.matter@hmrag.com
SOURCE: Journal of medicinal chemistry, (1999 Jun 3) 42 (11) 1908-20.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 20000303
Entered Medline: 19990624

ED Entered STN: 19990712
Last Updated on STN: 20000303
Entered Medline: 19990624

AB A set of 90 novel 2-(arylsulfonyl)-1,2,3, 4-**tetrahydroisoquinoline**-3-carboxylates and -**hydroxamates** as inhibitors of the **matrix metalloproteinase** human neutrophil collagenase (**MMP**-8) was designed, synthesized, and investigated by 3D-QSAR techniques (CoMFA, CoMSIA) and X-ray structure analysis. Docking studies of a reference compound are based on crystal structures of **MMP**-8 complexed with peptidic inhibitors to propose a model of its bioactive conformation. This model was validated by a 1. 7 A X-ray structure of the catalytic domain of **MMP**-8. The 3D-QSAR models based on a superposition rule derived from these docking studies were validated using conventional and cross-validated r2 values using the leave-one-out method, repeated analyses using two randomly chosen cross-validation groups plus randomization of biological activities. This led to consistent and highly predictive 3D-QSAR models with good correlation coefficients for both CoMFA and CoMSIA, which were found to correspond to experimentally determined **MMP**-8 catalytic site topology in terms of steric, electrostatic, and hydrophobic complementarity. Subsets selected as smaller training sets using 2D fingerprints and maximum dissimilarity methods resulted in 3D-QSAR models with remarkable correlation coefficients and a high predictive power. This allowed to compensate the weaker zinc binding properties of carboxylates by introducing optimal fitting P1' residues. The final QSAR information agrees with all experimental data for the binding topology and thus provides clear guidelines and accurate activity predictions for novel **MMP**-8 inhibitors.

CT Check Tags: Comparative Study
*Collagenases: AI, antagonists & inhibitors
Collagenases: CH, chemistry
Crystallography, X-Ray
Drug Design
Humans
Models, Molecular
Neutrophil Collagenase
*Protease Inhibitors: CH, chemistry

Protein Conformation
Structure-Activity Relationship
CN 0 (Protease Inhibitors); EC 3.4.24.- (Collagenases); EC 3.4.24.34 (Neutrophil Collagenase)

L51 ANSWER 19 OF 85 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 93341313 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8341137
TITLE: The phenytoin metabolite p-HPPH upregulates prostaglandin biosynthesis in human gingival fibroblasts challenged to interleukin-1.
AUTHOR: Brunius G; Iinuma M; Anduren I; Lerner U H; Modeer T
CORPORATE SOURCE: Department of Pedodontics, Faculty of Odontology, Karolinska Institutet, Huddinge, Sweden.
SOURCE: Life sciences, (1993) 53 (6) 503-15.
Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930917
Last Updated on STN: 19930917
Entered Medline: 19930831
ED Entered STN: 19930917
Last Updated on STN: 19930917
Entered Medline: 19930831
AB The effects of and interactions between the major phenytoin (PHT) metabolite 5-parahydroxyphenyl-5-phenylhydantoin (p-HPPH) and interleukin-1 (IL-1 alpha, IL-1 beta) or **tumor necrosis** factor alpha (**TNF** alpha) on prostaglandin biosynthesis in human gingival fibroblasts were studied. IL-1 alpha, IL-1 beta and **TNF** alpha, dose-dependently, stimulated PGE2 formation in gingival fibroblasts. The metabolite, p-HPPH (1.2-2.4 micrograms/ml), did not induce PGE2 formation itself but potentiated IL-1 alpha and IL1 beta induced PGE2 formation in the gingival fibroblasts in a manner dependent on the concentration of both IL-1 and p-HPPH. The metabolite also stimulated IL-1 induced formation of 6-Keto PGF1 alpha, the stable breakdown product of PGI2, in a dose dependent manner. IL-1 beta induces release of [3H]-arachidonic acid ([3H]-AA) from prelabelled fibroblasts, which was potentiated by p-HPPH (> or = 1.2 micrograms/ml). **TNF** alpha (> or = 1 ng/ml) significantly stimulated the biosynthesis of PGE2 by a process that was also potentiated by p-HPPH. Addition of exogenous, unlabelled AA (10 microM) caused an increase of PGE2 formation in the fibroblasts that was not potentiated by p-HPPH (1.6 micrograms/ml). The results indicate that treatment with p-HPPH results in upregulation of prostaglandin synthesis in gingival fibroblasts challenged to IL-1 or **TNF** alpha at the level of phospholipase A2.
CT Check Tags: Female; Male
Cells, Cultured
Child
Drug Synergism
Fibroblasts: ME, metabolism
Gingiva: CY, cytology
*Gingiva: DE, drug effects
Gingiva: ME, metabolism
Humans
*Interleukin-1: PD, pharmacology
***Phenytoin: AA, analogs & derivatives**
Phenytoin: PD, pharmacology

*Prostaglandins: BI, biosynthesis
Research Support, Non-U.S. Gov't
***Tumor Necrosis Factor-alpha: PD, pharmacology**
Up-Regulation: DE, drug effects
RN 2784-27-2 (hydroxyphenytoin); 57-41-0 (Phenytoin)
CN 0 (Interleukin-1); 0 (Prostaglandins); 0 (**Tumor Necrosis** Factor-alpha)

L51 ANSWER 20 OF 85 MEDLINE on STN
ACCESSION NUMBER: 2002652986 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12411982
TITLE: Plasma levels of **TNF**-alpha and IL-6 are inversely related to cytochrome P450-dependent drug metabolism in patients with congestive heart failure.
AUTHOR: Frye Reginald F; Schneider Virginia M; Frye Carole S; Feldman Arthur M
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Pharmacodynamic Research Center, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, USA.
SOURCE: Journal of cardiac failure, (2002 Oct) 8 (5) 315-9. Journal code: 9442138. ISSN: 1071-9164.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021105
Last Updated on STN: 20030306
Entered Medline: 20030305

ED Entered STN: 20021105
Last Updated on STN: 20030306
Entered Medline: 20030305

AB BACKGROUND: Cytochrome P450 (CYP) enzymes are important mediators of drug metabolism, and activity of these enzymes is a major determinant of the duration and intensity of drug effect. Circulating plasma concentrations of pro-inflammatory cytokines (e.g., **tumor necrosis** factor [**TNF**]-alpha and interleukin [IL]-6) are elevated in patients with heart failure and these cytokines have been shown to down-regulate CYP enzyme activity. The purpose of this study was to evaluate the relationship between plasma cytokine concentrations and CYP enzyme activities in patients with heart failure. METHODS AND RESULTS: Sixteen patients with congestive heart failure (New York Heart Association classes II-IV) received a metabolic probe cocktail consisting of caffeine, mephenytoin, dextromethorphan, and chlorzoxazone to assess the activities of the CYP enzymes 1A2, 2C19, 2D6, and 2E1. Blood and urine samples were collected for drug and metabolite determinations by high-performance liquid chromatography (HPLC); cytokine concentrations were measured by enzyme-linked immunosorbent assay (ELISA). We found a striking inverse relationship between both **TNF**-alpha and IL-6 plasma concentrations and the activity of CYP2C19; metabolism of caffeine (CYP1A2) also had a negative association with IL-6 plasma concentrations. CONCLUSIONS: Cytokine-mediated decreases in drug metabolism may contribute to observed variability in drug response and augment the risk of adverse drug effects in CHF patients.

CT Check Tags: Female; Male
Adult
Aged
Biological Markers: BL, blood
Cytochrome P-450 Enzyme System: DE, drug effects

Cytochrome P-450 Enzyme System: GE, genetics
*Cytochrome P-450 Enzyme System: ME, metabolism
Dextromethorphan: PD, pharmacology
Excitatory Amino Acid Antagonists: PD, pharmacology
Genetic Markers: DE, drug effects
Genetic Markers: GE, genetics
Genotype
Heart Failure, Congestive: GE, genetics
*Heart Failure, Congestive: ME, metabolism
Humans
*Interleukin-6: BL, blood
***Mephenytoin: AA, analogs & derivatives**
Mephenytoin: PD, pharmacology
Middle Aged
Mutation: DE, drug effects
Mutation: GE, genetics
Phenotype
Polymorphism, Genetic
Prevalence
Research Support, Non-U.S. Gov't
Statistics
***Tumor Necrosis Factor-alpha: ME, metabolism**
RN 125-71-3 (Dextromethorphan); 50-12-4 (Mephenytoin); 61837-65-8 (4-hydroxymephenytoin); 9035-51-2 (Cytochrome P-450 Enzyme System)
CN 0 (Biological Markers); 0 (Excitatory Amino Acid Antagonists); 0 (Genetic Markers); 0 (Interleukin-6); 0 (**Tumor Necrosis** Factor-alpha)

L51 ANSWER 21 OF 85 MEDLINE on STN
ACCESSION NUMBER: 96251432 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8653494
TITLE: Effect of phenytoin on interleukin-1 beta production in human gingival fibroblasts challenged to **tumor necrosis** factor alpha in vitro.
AUTHOR: Brunius G; Yucel-Lindberg T; Shinoda K; Modeer T
CORPORATE SOURCE: Department of Orthodontics and Pediatric Dentistry, Faculty of Odontology, Karolinska Institutet, Huddinge, Sweden.
SOURCE: European journal of oral sciences, (1996 Feb) 104 (1) 27-33.
Journal code: 9504563. ISSN: 0909-8836.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960808
Last Updated on STN: 19970203
Entered Medline: 19960801
ED Entered STN: 19960808
Last Updated on STN: 19970203
Entered Medline: 19960801
AB Effects and interaction of **tumor necrosis** factor alpha (**TNF** alpha) and the antiepileptic drug phenytoin (PHT) on interleukin-1 beta (IL-1 beta) production as well as on prostaglandin E2 (PGE2) formation were studied in gingival fibroblasts in vitro. **TNF** alpha, in contrast to PHT, dose-dependently stimulated the production of cell-associated IL-1 beta. The stimulatory effect of **TNF** alpha on IL-1 beta production was accompanied by enhanced PGE2 formation. When PHT and **TNF** alpha were added simultaneously, the drug potentiated the stimulatory effect of **TNF** alpha on both

IL-1 beta production and PGE2 formation. The major PHT metabolite, p-HPPH, did not affect IL-1 beta production, either alone or in combination with **TNF** alpha. The production of IL-1 beta induced by **TNF** alpha and the combination of **TNF** alpha and PHT was further enhanced in the presence of the prostaglandin endoperoxide (PGH) synthase inhibitors, indomethacin and flurbiprofen. The PHT-mediated enhancement of **TNF** alpha-induced IL-1 beta production and PGE2 formation in gingival fibroblasts may be an important link in the pathogenesis of gingival overgrowth induced by PHT.

CT Child
Cyclooxygenase Inhibitors: ME, metabolism
Cyclooxygenase Inhibitors: PD, pharmacology
Dinoprostone: BI, biosynthesis
Dose-Response Relationship, Drug
Drug Synergism
Fibroblasts: DE, drug effects
Fibroblasts: ME, metabolism
Flurbiprofen: PD, pharmacology
Gingiva: CY, cytology
*Gingiva: DE, drug effects
Gingiva: ME, metabolism
Gingival Hyperplasia: CI, chemically induced
Gingival Hyperplasia: ME, metabolism
Humans
Indomethacin: PD, pharmacology
*Interleukin-1: BI, biosynthesis
Phenytoin: AA, analogs & derivatives
*Phenytoin: PD, pharmacology
Research Support, Non-U.S. Gov't
***Tumor Necrosis Factor-alpha: PD, pharmacology**
Up-Regulation

RN 2784-27-2 (hydroxyphenytoin); 363-24-6 (Dinoprostone); 5104-49-4 (Flurbiprofen); 53-86-1 (Indomethacin); 57-41-0 (Phenytoin)

CN 0 (Cyclooxygenase Inhibitors); 0 (Interleukin-1); 0 (**Tumor Necrosis** Factor-alpha)

L51 ANSWER 22 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 1

ACCESSION NUMBER: 2004378690 EMBASE
TITLE: The evolution of the **matrix metalloproteinase** inhibitor drug discovery program at Abbott Laboratories.
AUTHOR: Wada C.K.
CORPORATE SOURCE: C.K. Wada, Abbott Laboratories, Dept. R47J, 100 Abbott Park Rd., Abbott Park, IL 60064-6100, United States. carol.k.wada@abbott.com
SOURCE: Current Topics in Medicinal Chemistry, (2004) Vol. 4, No. 12, pp. 1255-1267.
Refs: 24
ISSN: 1568-0266 CODEN: CTMCCL
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040924

Last Updated on STN: 20040924

ED Entered STN: 20040924
Last Updated on STN: 20040924

AB **Matrix metalloproteinases** (**MMPs**) have been implicated in several pathologies. At Abbott Laboratories, the **matrix metalloproteinases** inhibitor drug discovery program has focused on the discovery of a potent, selective, orally bioavailable **MMP** inhibitor for the treatment of cancer. The program evolved from early succinate-based inhibitors to utilizing in-house technology such as SAR by NMR to develop a novel class of biaryl **hydroxamate MMP** inhibitors. The metabolic instability of the biaryl **hydroxamates** led to the discovery of a new class of N-formylhydroxylamine (**retrohydroxamate**) biaryl ethers, exemplified by ABT-770 (16). Toxicity issues with this pre-clinical candidate led to the discovery of another novel class of **retrohydroxamate MMP** inhibitors, the **phenoxyphenyl** sulfones such as ABT-518 (19j). ABT-518 is a potent, orally bioavailable, selective inhibitor of **MMP**-2 and 9 over **MMP**-1 that has been evaluated in Phase I clinical trials in cancer patients. .COPYRGT. 2004 Bentham Science Publishers Ltd.

CT Medical Descriptors:
enzyme inhibition
drug structure
drug synthesis
drug design
structure activity relation
structure analysis
drug selectivity
drug bioavailability
drug potency
nuclear magnetic resonance
drug classification
drug half life
in vitro study
in vivo study
melanoma: DT, drug therapy
antineoplastic activity
cancer inhibition
cancer model
drug clearance
toxicity testing
human
nonhuman
mouse
clinical trial
review
Drug Descriptors:
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: CM, drug comparison**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: DT, drug therapy**
***matrix metalloproteinase inhibitor: TO, drug toxicity**
***matrix metalloproteinase inhibitor: PK, pharmacokinetics**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: IV, intravenous drug administration**
***matrix metalloproteinase inhibitor: PO, oral drug administration**
succinic acid derivative: CT, clinical trial
succinic acid derivative: AN, drug analysis

succinic acid derivative: CM, drug comparison
succinic acid derivative: DV, drug development
succinic acid derivative: DT, drug therapy
succinic acid derivative: PK, pharmacokinetics
succinic acid derivative: PD, pharmacology
succinic acid derivative: IV, intravenous drug administration
succinic acid derivative: PO, oral drug administration
hydroxamic acid derivative: CT, clinical trial
hydroxamic acid derivative: AN, drug analysis
hydroxamic acid derivative: CM, drug comparison
hydroxamic acid derivative: DV, drug development
hydroxamic acid derivative: DT, drug therapy
hydroxamic acid derivative: PK, pharmacokinetics
hydroxamic acid derivative: PD, pharmacology
hydroxamic acid derivative: IV, intravenous drug administration
hydroxamic acid derivative: PO, oral drug administration
gelatinase A: EC, endogenous compound
gelatinase B: EC, endogenous compound
interstitial collagenase: EC, endogenous compound
matrilysin: EC, endogenous compound
abt 770: AN, drug analysis
abt 770: CM, drug comparison
abt 770: DV, drug development
abt 770: DT, drug therapy
abt 770: TO, drug toxicity
abt 770: PK, pharmacokinetics
abt 770: PD, pharmacology
abt 770: IV, intravenous drug administration
abt 770: PO, oral drug administration
abt 518: CT, clinical trial
abt 518: AN, drug analysis
abt 518: CM, drug comparison
abt 518: DV, drug development
abt 518: DT, drug therapy
abt 518: PK, pharmacokinetics
abt 518: PD, pharmacology
abt 518: PO, oral drug administration
metalloproteinase inhibitor: CT, clinical trial
metalloproteinase inhibitor: AN, drug analysis
metalloproteinase inhibitor: CM, drug comparison
metalloproteinase inhibitor: DV, drug development
metalloproteinase inhibitor: DT, drug therapy
metalloproteinase inhibitor: TO, drug toxicity
metalloproteinase inhibitor: PK, pharmacokinetics
metalloproteinase inhibitor: PD, pharmacology
metalloproteinase inhibitor: IV, intravenous drug administration
metalloproteinase inhibitor: PO, oral drug administration
batimastat: AN, drug analysis
batimastat: CM, drug comparison
batimastat: DV, drug development
batimastat: PK, pharmacokinetics
batimastat: PD, pharmacology
batimastat: IV, intravenous drug administration
batimastat: PO, oral drug administration
macrocyclic compound: AN, drug analysis
macrocyclic compound: CM, drug comparison
macrocyclic compound: DV, drug development
macrocyclic compound: PD, pharmacology
macrocyclic compound: IV, intravenous drug administration
indole derivative: AN, drug analysis

indole derivative: CM, drug comparison
indole derivative: DV, drug development
indole derivative: PD, pharmacology
ketone derivative: AN, drug analysis
ketone derivative: CM, drug comparison
ketone derivative: DV, drug development
ketone derivative: PD, pharmacology
ketone derivative: IV, intravenous drug administration
pyrrole derivative: AN, drug analysis
pyrrole derivative: CM, drug comparison
pyrrole derivative: DV, drug development
pyrrole derivative: PD, pharmacology
benzophenone: AN, drug analysis
benzophenone: CM, drug comparison
benzophenone: DV, drug development
benzophenone: PD, pharmacology
stromelysin inhibitor: AN, drug analysis
stromelysin inhibitor: CM, drug comparison
stromelysin inhibitor: DV, drug development

CT Drug Descriptors:
stromelysin inhibitor: PD, pharmacology
stromelysin: EC, endogenous compound
hydantoin derivative: AN, drug analysis
hydantoin derivative: CM, drug comparison
hydantoin derivative: DV, drug development
hydantoin derivative: PK, pharmacokinetics
hydantoin derivative: PD, pharmacology
hydantoin derivative: IV, intravenous drug administration
hydantoin derivative: PO, oral drug administration
neutrophil collagenase: EC, endogenous compound
collagenase 3: EC, endogenous compound
unclassified drug

RN (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (matrilysin) 141256-52-2; (batimastat) 130370-60-4, 130464-84-5; (benzophenone) 119-61-9; (stromelysin) 79955-99-0; (collagenase 3) 175449-82-8
CN (1) Abt 770; (2) Abt 518
CO (2) Abbott

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ACCESSION NUMBER: 2005090790 EMBASE
TITLE: Recent developments in the design of specific **matrix metalloproteinase** inhibitors aided by structural and computational studies.
AUTHOR: Rao B.G.
CORPORATE SOURCE: B.G. Rao, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139, United States. govinda_rao@vrtx.com
SOURCE: Current Pharmaceutical Design, (2005) Vol. 11, No. 3, pp. 295-322.
Refs: 133
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050310
Last Updated on STN: 20050310

ED Entered STN: 20050310
Last Updated on STN: 20050310

AB It has been 10 years since a 3-dimensional structure of the catalytic domain of a **Matrix Metalloprotease** (**MMP**) was revealed for the first time in 1994. More than 80 structures of different **MMPs** in apo and inhibited forms, determined by X-ray crystallography and NMR methods, have been published by the end of year 2003. A large number of very potent inhibitors have been disclosed in published and patent literature. Several **MMP** inhibitors entered clinical trials for the treatment of cancer and arthritis. Most of the first generation inhibitors have **hydroxamic** acid as the Zinc-binding group and have limited specificity. With the failure of these inhibitors in clinical trials, more efforts have been directed to the design of specific inhibitors with different Zn-binding groups in recent years. This review will summarize all the published structural information and focus on the inhibitors that were designed to take advantage of the nonprime side of the **MMP** active site using structural information and computational analysis. Representative structures from all **MMPs** are aligned to a target structure to provide a better understanding of the similarities and differences of the active site pockets. This analysis supports the view that the differences in the nonprime side pockets provide better opportunities for designing inhibitors with higher specificity. Published information on all the Zinc-binding groups of **MMP** inhibitors is reviewed for the first time. Pros and cons of inhibitors with non-**hydroxamate** Zinc-binding groups in terms of specificity, toxicity and pharmacokinetic properties are discussed.

CT Medical Descriptors:
*computer aided design
*drug design
drug structure
structure analysis
computer analysis
three dimensional imaging
protein domain
X ray crystallography
nuclear magnetic resonance
cancer chemotherapy
arthritis: DT, drug therapy
drug binding
binding site
drug specificity
drug targeting
protein targeting
pancreas cancer: DT, drug therapy
osteoarthritis: DT, drug therapy
solid tumor: DT, drug therapy
musculoskeletal disease: SI, side effect
arthralgia: SI, side effect
myalgia: SI, side effect
Kaposi sarcoma: DT, drug therapy
drug half life
drug selectivity
human
clinical trial
review

priority journal
Drug Descriptors:
***matrix metalloproteinase inhibitor: AE, adverse drug reaction**
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: CM, drug comparison**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: DT, drug therapy**
***matrix metalloproteinase inhibitor: TO, drug toxicity**
***matrix metalloproteinase inhibitor: PK, pharmacokinetics**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: PO, oral drug administration**
matrix metalloproteinase: EC, endogenous compound
hydroxamic acid
zinc
collagenase: EC, endogenous compound
gelatinase A: EC, endogenous compound
stromelysin: EC, endogenous compound
matrilysin: EC, endogenous compound
gelatinase B: EC, endogenous compound
stromelysin 3: EC, endogenous compound
stromelysin 2: EC, endogenous compound
macrophage elastase: EC, endogenous compound
collagenase 3: EC, endogenous compound
batimastat: AE, adverse drug reaction
batimastat: CT, clinical trial
batimastat: AN, drug analysis
batimastat: CM, drug comparison
batimastat: DT, drug therapy
batimastat: PO, oral drug administration
marimastat: AE, adverse drug reaction
marimastat: CT, clinical trial
marimastat: AN, drug analysis
marimastat: CM, drug comparison
marimastat: DT, drug therapy
solimastat: CT, clinical trial
solimastat: AN, drug analysis
solimastat: CM, drug comparison
solimastat: DT, drug therapy
prinomastat: CT, clinical trial
prinomastat: AN, drug analysis
prinomastat: CM, drug comparison
prinomastat: DT, drug therapy
cgs 27023a: AE, adverse drug reaction
cgs 27023a: CT, clinical trial
cgs 27023a: AN, drug analysis
cgs 27023a: CM, drug comparison
cgs 27023a: DT, drug therapy
cipemastat: CT, clinical trial
cipemastat: AN, drug analysis
cipemastat: CM, drug comparison
cipemastat: DT, drug therapy
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CT, clinical trial
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: AN, drug analysis
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CM, drug comparison
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: DT, drug therapy

tanomastat: CT, clinical trial
tanomastat: AN, drug analysis
tanomastat: CM, drug comparison
tanomastat: DT, drug therapy
d 2163: CT, clinical trial
d 2163: AN, drug analysis
d 2163: CM, drug comparison
d 2163: DT, drug therapy
4 dedimethylaminosancycline: CT, clinical trial
4 dedimethylaminosancycline: AN, drug analysis
4 dedimethylaminosancycline: CM, drug comparison
4 dedimethylaminosancycline: DT, drug therapy
abt 518: CT, clinical trial
abt 518: AN, drug analysis
abt 518: CM, drug comparison
abt 518: DT, drug therapy
abt 518: PK, pharmacokinetics
s 3304: CT, clinical trial
s 3304: AN, drug analysis
s 3304: CM, drug comparison
s 3304: DT, drug therapy
antineoplastic agent: CT, clinical trial
antineoplastic agent: AN, drug analysis
antineoplastic agent: CM, drug comparison
antineoplastic agent: DT, drug therapy
antineoplastic agent: PK, pharmacokinetics
tetracycline derivative: CT, clinical trial
tetracycline derivative: DT, drug therapy
fibronectin: EC, endogenous compound
zinc ion: EC, endogenous compound
unindexed drug
unclassified drug

RN (zinc) 7440-66-6; (collagenase) 37288-86-1, 39433-96-0, 9001-12-1; (gelatinase A) 146480-35-5; (stromelysin) 79955-99-0; (matrilysin) 141256-52-2; (gelatinase B) 146480-36-6; (stromelysin 3) 145267-01-2; (stromelysin 2) 140610-48-6; (collagenase 3) 175449-82-8; (batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (cgs 27023a) 169799-04-6; (cipemastat) 190648-49-8; (4 [[[4 (4 chlorophenoxy)**phenyl**]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (tanomastat) 179545-76-7, 179545-77-8; (d 2163) 191537-76-5; (4 dedimethylaminosancycline) 15866-90-7; (fibronectin) 86088-83-7; (zinc ion) 23713-49-7

CN (1) Bb 94; (2) Bb 2516; (3) Bb 3644; (4) Ag 3340; (5) Cgs 27023a; (6) Ro 32 3555; (7) Rs 130830; (8) Abt 518; (9) Bay 12 9566; (10) S 3304

CO (3) British Biotechnology; (4) Agouron; (5) Novartis; (7) Hoffmann La Roche; (8) Abbott; (9) Bayer; (10) Shionogi

L51 ANSWER 24 OF 85 EMBASE

ACCESSION NUMBER: 2004378692 EMBASE
TITLE: The design and synthesis of aryl **hydroxamic** acid inhibitors of **MMPs** and **TACE.**
AUTHOR: Levin J.I.
CORPORATE SOURCE: J.I. Levin, Wyeth Research, 401 N. Middlestown Road, Pearl River, NY 10965, United States. levinji@wyeth.com
SOURCE: Current Topics in Medicinal Chemistry, (2004) Vol. 4, No. 12, pp. 1289-1310.
Refs: 60
ISSN: 1568-0266 CODEN: CTMCCL

COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040924
Last Updated on STN: 20040924
ED Entered STN: 20040924
Last Updated on STN: 20040924
AB Three different classes of aryl **hydroxamic** acid scaffolds have been explored and provided potent inhibitors of **MMP**-1, -2, -9, -13 and **TACE**. Structure-based design has allowed the evolution of these inhibitors from broad spectrum inhibitors into compounds that are more selective for **MMPs** relevant to particular disease states. Aryl **hydroxamates** selective for **MMP**-9, **MMP** -13 and **TACE** have been disclosed that may aid in the study of the physiological role of these enzymes. Furthermore, the different selectivity profiles offered by these **MMP**/**TACE** inhibitors may allow the determination of which metalloprotease, or group of metalloproteases, must be inhibited for the safe, long-term treatment of osteoarthritis, rheumatoid arthritis and cancer. Some of these compounds have demonstrated useful biological activity in efficacy models relevant to osteoarthritis and rheumatoid arthritis and are therefore potential clinical candidates. .COPYRGT. 2004 Bentham Science Pubishers Ltd.
CT Medical Descriptors:
drug design
drug synthesis
enzyme inhibition
drug structure
structure analysis
drug potency
drug selectivity
drug safety
long term care
osteoarthritis: DT, drug therapy
rheumatoid arthritis: DT, drug therapy
cancer therapy
drug efficacy
cancer inhibition
antineoplastic activity
musculoskeletal disease: SI, side effect
structure activity relation
high throughput screening
human
nonhuman
mouse
clinical trial
review
Drug Descriptors:
*hydroxamic acid derivative: AE, adverse drug reaction
*hydroxamic acid derivative: CT, clinical trial
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: CM, drug comparison
*hydroxamic acid derivative: DV, drug development

*hydroxamic acid derivative: DT, drug therapy
*hydroxamic acid derivative: PD, pharmacology
*hydroxamic acid derivative: IP, intraperitoneal drug administration
***hydroxamic acid derivative: PO, oral drug administration**
***matrix metalloproteinase inhibitor: AE, adverse drug reaction**
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: CM, drug comparison**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: DT, drug therapy**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: IP, intraperitoneal drug administration**
***matrix metalloproteinase inhibitor: PO, oral drug administration**
***tumor necrosis factor alpha converting enzyme inhibitor: AN, drug analysis**
***tumor necrosis factor alpha converting enzyme inhibitor: CM, drug comparison**
***tumor necrosis factor alpha converting enzyme inhibitor: DV, drug development**
***tumor necrosis factor alpha converting enzyme inhibitor: DT, drug therapy**
***tumor necrosis factor alpha converting enzyme inhibitor: PD, pharmacology**
***tumor necrosis factor alpha converting enzyme inhibitor: PO, oral drug administration**
matrix metalloproteinase: EC, endogenous compound
tumor necrosis factor alpha converting enzyme: EC, endogenous compound
interstitial collagenase: EC, endogenous compound
gelatinase A: EC, endogenous compound
gelatinase B: EC, endogenous compound
collagenase 3: EC, endogenous compound
stromelysin inhibitor: AE, adverse drug reaction
stromelysin inhibitor: CT, clinical trial
stromelysin inhibitor: AN, drug analysis
stromelysin inhibitor: CM, drug comparison
stromelysin inhibitor: DT, drug therapy
stromelysin inhibitor: PD, pharmacology
cgs 27023a: AE, adverse drug reaction
cgs 27023a: CT, clinical trial
cgs 27023a: AN, drug analysis
cgs 27023a: CM, drug comparison
cgs 27023a: DT, drug therapy
cgs 27023a: PD, pharmacology
cgs 27023a: PO, oral drug administration
marimastat: AE, adverse drug reaction
marimastat: CT, clinical trial
marimastat: AN, drug analysis
marimastat: CM, drug comparison
marimastat: DT, drug therapy
marimastat: PD, pharmacology
cipemastat: AE, adverse drug reaction
cipemastat: CT, clinical trial
cipemastat: AN, drug analysis
cipemastat: CM, drug comparison
cipemastat: DT, drug therapy
cipemastat: PD, pharmacology
prinomastat: AE, adverse drug reaction
prinomastat: CT, clinical trial

prinomastat: AN, drug analysis
prinomastat: CM, drug comparison
prinomastat: DT, drug therapy
prinomastat: PD, pharmacology
anthranilic acid derivative: AE, adverse drug reaction
anthranilic acid derivative: CT, clinical trial
anthranilic acid derivative: AN, drug analysis
anthranilic acid derivative: CM, drug comparison
anthranilic acid derivative: DT, drug therapy
anthranilic acid derivative: PD, pharmacology
anthranilic acid derivative: IP, intraperitoneal drug administration
piperidine derivative: AN, drug analysis
piperidine derivative: CM, drug comparison
piperidine derivative: DV, drug development
piperidine derivative: PD, pharmacology
piperazine derivative: AN, drug analysis
piperazine derivative: CM, drug comparison
piperazine derivative: DV, drug development
piperazine derivative: PD, pharmacology
sulfonamide: AN, drug analysis
sulfonamide: CM, drug comparison
sulfonamide: DV, drug development
sulfonamide: PD, pharmacology
sulfonamide: PO, oral drug administration
aniline derivative: AN, drug analysis
aniline derivative: CM, drug comparison
aniline derivative: DV, drug development
aniline derivative: PD, pharmacology
pyridine derivative: AN, drug analysis
pyridine derivative: CM, drug comparison
pyridine derivative: DV, drug development
pyridine derivative: PD, pharmacology
thiophene derivative: AN, drug analysis
thiophene derivative: CM, drug comparison
thiophene derivative: DV, drug development
thiophene derivative: PD, pharmacology

CT Drug Descriptors:

pyrazole derivative: AN, drug analysis
pyrazole derivative: CM, drug comparison
pyrazole derivative: DV, drug development
pyrazole derivative: PD, pharmacology
cyclohexane derivative: AN, drug analysis
cyclohexane derivative: CM, drug comparison
cyclohexane derivative: DV, drug development
cyclohexane derivative: PD, pharmacology
quinoline derivative: AN, drug analysis
quinoline derivative: CM, drug comparison
quinoline derivative: DV, drug development
quinoline derivative: PD, pharmacology
quinoline derivative: PO, oral drug administration
isoxazole derivative: AN, drug analysis
isoxazole derivative: CM, drug comparison
isoxazole derivative: DV, drug development
isoxazole derivative: PD, pharmacology
isothiazole derivative: AN, drug analysis
isothiazole derivative: CM, drug comparison
isothiazole derivative: DV, drug development
isothiazole derivative: PD, pharmacology
pyrazolopyrimidine derivative: AN, drug analysis
pyrazolopyrimidine derivative: CM, drug comparison

pyrazolopyrimidine derivative: DV, drug development
pyrazolopyrimidine derivative: PD, pharmacology
benzofuran derivative: AN, drug analysis
benzofuran derivative: CM, drug comparison
benzofuran derivative: DV, drug development
benzofuran derivative: PD, pharmacology
benzothiophene derivative: AN, drug analysis
benzothiophene derivative: CM, drug comparison
benzothiophene derivative: DV, drug development
benzothiophene derivative: PD, pharmacology
unindexed drug

RN (**tumor necrosis** factor **alpha converting** enzyme) 151769-16-3; (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (collagenase 3) 175449-82-8; (cgs 27023a) 169799-04-6; (marimastat) 154039-60-8; (cipemastat) 190648-49-8; (prinomastat) 192329-42-3, 195008-93-6

CN Cgs 27023a; Ro 32 3555; Ag 3340

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ACCESSION NUMBER: 2004026493 EMBASE
TITLE: Cyclic sulfone **hydroxamates** as inhibitors of **matrix metalloproteinases** and/or **TNF**-α -**converting** enzymes.
SOURCE: Expert Opinion on Therapeutic Patents, (2004) Vol. 14, No. 1, pp. 121-124.
Refs: 15
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040129
Last Updated on STN: 20040129

ED Entered STN: 20040129
Last Updated on STN: 20040129

AB A series of cyclic sulfone-based **hydroxamates** are claimed to be inhibitors of **matrix metalloproteinases** (**MMPs**) and **TNF**-α -**converting** enzyme (**TACE**). Synthesis of one representative example is described. No biological data are given but these compounds are claimed to inhibit **MMPs**, **TACE** and aggrecanase. These compounds might be useful to treat chronic diseases such as arthritis and cancer.

CT Medical Descriptors:
drug synthesis
chronic disease: DT, drug therapy
drug structure
osteoarthritis: DT, drug therapy
rheumatoid arthritis: DT, drug therapy
physical chemistry
patent
drug selectivity
drug mechanism
arthritis: DT, drug therapy
cancer chemotherapy
human

clinical trial
article
Drug Descriptors:
*sulfone derivative: CT, clinical trial
*sulfone derivative: AN, drug analysis
*sulfone derivative: DV, drug development
*sulfone derivative: DT, drug therapy
*sulfone derivative: PD, pharmacology
*hydroxamic acid derivative: CT, clinical trial
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: DV, drug development
*hydroxamic acid derivative: DT, drug therapy
*hydroxamic acid derivative: PD, pharmacology
matrix metalloproteinase inhibitor: CT, clinical trial
matrix metalloproteinase inhibitor: AN, drug analysis
matrix metalloproteinase inhibitor: DV, drug development
matrix metalloproteinase inhibitor: DT, drug therapy
matrix metalloproteinase inhibitor: PD, pharmacology
prinomasta: AN, drug analysis
prinomasta: DV, drug development
prinomasta: PD, pharmacology
ro 327315: AN, drug analysis
ro 327315: DV, drug development
ro 327315: PD, pharmacology
dpc 333: CT, clinical trial
dpc 333: AN, drug analysis
dpc 333: DV, drug development
dpc 333: DT, drug therapy
dpc 333: PD, pharmacology
bms 561392: CT, clinical trial
bms 561392: AN, drug analysis
bms 561392: DV, drug development
bms 561392: DT, drug therapy
bms 561392: PD, pharmacology
tumor necrosis factor alpha converting enzyme inhibitor: CT, clinical trial
tumor necrosis factor alpha converting enzyme inhibitor: AN, drug analysis
tumor necrosis factor alpha converting enzyme inhibitor: DV, drug development
tumor necrosis factor alpha converting enzyme inhibitor: DT, drug therapy
tumor necrosis factor alpha converting enzyme inhibitor: PD, pharmacology
matrix metalloproteinase: EC, endogenous compound
tumor necrosis factor alpha converting enzyme: EC, endogenous compound
aggrecanase: EC, endogenous compound
etanercept: PD, pharmacology
infliximab: PD, pharmacology
adalimumab: PD, pharmacology
tumor necrosis factor antibody: PD, pharmacology
tumor necrosis factor antibody: PO, oral drug administration
marimastat: AN, drug analysis
marimastat: DV, drug development
marimastat: PD, pharmacology
cipemastat: AN, drug analysis
cipemastat: DV, drug development
cipemastat: PD, pharmacology
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4

carbohydroxamic acid: AN, drug analysis
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4
carbohydroxamic acid: DV, drug development
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4
carbohydroxamic acid: PD, pharmacology
tanomastat: AN, drug analysis
tanomastat: DV, drug development
tanomastat: PD, pharmacology
d 2163: AN, drug analysis
d 2163: DV, drug development
d 2163: PD, pharmacology
unclassified drug

RN (**tumor necrosis** factor **alpha converting** enzyme) 151769-16-3; (aggrecanase) 147172-61-0; (etanercept) 185243-69-0, 200013-86-1; (infliximab) 170277-31-3; (adalimumab) 331731-18-1; (**tumor necrosis** factor antibody) 162774-06-3; (marimastat) 154039-60-8; (cipemastat) 190648-49-8; (4 [[[4 (4 chlorophenoxy)**phenyl**]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (tanomastat) 179545-76-7, 179545-77-8; (d 2163) 191537-76-5

CN (1) Enbrel; (2) Enbrel; (3) Remicade; (4) Bms 275291; (5) Bms 561392; (6) D 2163; Rs 130830; Bay 129566; Ro 327315; Dpc 333

CO (1) Amgen; (2) Wyeth; (3) Centocor; (6) Bristol Myers Squibb

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ACCESSION NUMBER: 2003193795 EMBASE
TITLE: **Matrix metalloproteinase** inhibitors (MMPIs): The beginning of phase I or the termination of phase III clinical trials.
AUTHOR: Pavlaki M.; Zucker S.
CORPORATE SOURCE: M. Pavlaki, Department of Medicine, School of Medicine, Stt. Univ. of NY at Stony Brook, Stony Brook, NY 11794, United States. s_zucker@yahoo.com
SOURCE: Cancer and Metastasis Reviews, (2003) Vol. 22, No. 2-3, pp. 177-203.
Refs: 210
ISSN: 0167-7659 CODEN: CMRED4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030529
Last Updated on STN: 20030529

ED Entered STN: 20030529
Last Updated on STN: 20030529

AB The decade of the 1990s was ripe with enthusiasm for the use of MMPIs to treat cancer. Limitations to new cytotoxic chemotherapy approaches to treat solid cancers and a better understanding of tumor biology provided a strong impetus for alternative drug development. It is estimated that the pharmaceutical industry invested at least a billion dollars in this effort. Because MMPIs represent an entirely different therapeutic modality from proven anti-cancer agents, many of the therapeutic trials designed to test MMPIs in human patients with cancer bypassed traditional approaches to evaluate drug efficiency. The concept of systematic progression from small phase I (dose escalation to toxicity to examine

drug safety), to phase II (drug treatment of patients with cancer types considered to be good candidates for the selected drug), to phase III (randomized trial of new drug versus best available therapy to determine drug efficacy) trials was modified. Much to the chagrin of everyone involved in these studies, the randomized trials of MMPIs in advanced cancer have, pretty much, flopped. This review article will attempt to dissect out aspects of previous human and animal studies that may be helpful in making decisions about the future of MMPI drug development for the treatment of cancer. The important questions to be addressed in this report are: What are the lessons that we have learned from preclinical (animal models) and clinical studies of MMPIs in cancer? Are we ready to abandon MMPIs as a therapeutic modality in cancer (termination of phase III trials) or do we need to have a better understanding of the myriad effects of **MMPs** in cancer before we proceed to develop different types of drugs that alter **MMP** activity in patients with cancer (beginning of new phase I trials)?

CT Medical Descriptors:
*solid tumor: DT, drug therapy
drug industry
cancer chemotherapy
drug efficacy
drug safety
advanced cancer
drug activity
drug structure
cancer growth
drug potentiation
treatment outcome
side effect: SI, side effect
tendinitis: SI, side effect
arthralgia: SI, side effect
muscle rigidity: SI, side effect
edema: SI, side effect
skin discoloration: SI, side effect
thrombocytopenia: SI, side effect
enzyme defect: SI, side effect
nausea: SI, side effect
rash: SI, side effect
thromboembolism: SI, side effect
myalgia: SI, side effect
human
nonhuman
clinical trial
phase 1 clinical trial
phase 3 clinical trial
review
priority journal
Drug Descriptors:
***matrix metalloproteinase inhibitor: AE, adverse drug reaction**
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: CB, drug combination**
***matrix metalloproteinase inhibitor: IT, drug interaction**
***matrix metalloproteinase inhibitor: DT, drug therapy**
***matrix metalloproteinase inhibitor: PK, pharmacokinetics**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: IP, intraperitoneal drug administration**
***matrix metalloproteinase inhibitor: PL, intrapleural drug administration**
***matrix metalloproteinase inhibitor: PO, oral drug administration**

matrix metalloproteinase: EC, endogenous compound
batimastat: AE, adverse drug reaction
batimastat: CT, clinical trial
batimastat: DT, drug therapy
batimastat: PD, pharmacology
batimastat: IP, intraperitoneal drug administration
batimastat: PL, intrapleural drug administration
tanomastat: CT, clinical trial
tanomastat: CB, drug combination
tanomastat: CM, drug comparison
tanomastat: IT, drug interaction
tanomastat: DT, drug therapy
tanomastat: PD, pharmacology
tanomastat: PO, oral drug administration
prinomastat: CT, clinical trial
prinomastat: CB, drug combination
prinomastat: IT, drug interaction
prinomastat: DT, drug therapy
prinomastat: PD, pharmacology
prinomastat: IP, intraperitoneal drug administration
prinomastat: PO, oral drug administration
marimastat: AE, adverse drug reaction
marimastat: CT, clinical trial
marimastat: CB, drug combination
marimastat: CM, drug comparison
marimastat: CR, drug concentration
marimastat: DO, drug dose
marimastat: IT, drug interaction
marimastat: DT, drug therapy
marimastat: PK, pharmacokinetics
marimastat: PD, pharmacology
marimastat: PO, oral drug administration
marimastat: SC, subcutaneous drug administration
cytotoxic agent: CT, clinical trial
cytotoxic agent: CB, drug combination
cytotoxic agent: IT, drug interaction
cytotoxic agent: DT, drug therapy
cytotoxic agent: PD, pharmacology
cisplatin: CB, drug combination
cisplatin: IT, drug interaction
cisplatin: DT, drug therapy
cisplatin: PD, pharmacology
doxorubicin: CB, drug combination
doxorubicin: IT, drug interaction
doxorubicin: DT, drug therapy
doxorubicin: PD, pharmacology
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide: CB, drug combination
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide: IT, drug interaction
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide: DT, drug therapy
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide: PD, pharmacology
n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 chlorophenyl)propyl] n4 hydroxybutanediamide: SC, subcutaneous drug administration
gemcitabine: CT, clinical trial
gemcitabine: CB, drug combination
gemcitabine: CM, drug comparison
gemcitabine: IT, drug interaction

gemcitabine: DT, drug therapy
gemcitabine: PD, pharmacology
gemcitabine: IV, intravenous drug administration
ae 941: CT, clinical trial
ae 941: DT, drug therapy
ae 941: PD, pharmacology
angiogenesis inhibitor: DT, drug therapy
angiogenesis inhibitor: PD, pharmacology
tetracycline derivative: DT, drug therapy
tetracycline derivative: PD, pharmacology
4 dedimethylaminosancycline: AE, adverse drug reaction
4 dedimethylaminosancycline: CT, clinical trial
4 dedimethylaminosancycline: DT, drug therapy
4 dedimethylaminosancycline: PD, pharmacology
4 dedimethylaminosancycline: PO, oral drug administration
d 2163: AE, adverse drug reaction
d 2163: CT, clinical trial
d 2163: CB, drug combination
d 2163: DT, drug therapy
d 2163: PD, pharmacology
hydroxamic acid derivative: AE, adverse drug reaction

CT Drug Descriptors:
hydroxamic acid derivative: CT, clinical trial
hydroxamic acid derivative: DT, drug therapy
hydroxamic acid derivative: PD, pharmacology
hydroxamic acid derivative: PL, intrapleural drug administration
hydroxamic acid derivative: PO, oral drug administration
cgs 27023a: AE, adverse drug reaction
cgs 27023a: CT, clinical trial
cgs 27023a: DT, drug therapy
cgs 27023a: PD, pharmacology
placebo
temozolomide: AE, adverse drug reaction
temozolomide: CT, clinical trial
temozolomide: CB, drug combination
temozolomide: CM, drug comparison
temozolomide: IT, drug interaction
temozolomide: DT, drug therapy
temozolomide: PD, pharmacology
fluorouracil: CT, clinical trial
fluorouracil: CB, drug combination
fluorouracil: CM, drug comparison
fluorouracil: IT, drug interaction
fluorouracil: DT, drug therapy
fluorouracil: PD, pharmacology
cipemastat: CT, clinical trial
cipemastat: DT, drug therapy
cipemastat: PD, pharmacology
paclitaxel: CT, clinical trial
paclitaxel: CB, drug combination
paclitaxel: DT, drug therapy
paclitaxel: PD, pharmacology
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
carboplatin: PD, pharmacology
ilomastat: DT, drug therapy
ilomastat: PD, pharmacology

RN (batimastat) 130370-60-4, 130464-84-5; (tanomastat) 179545-76-7, 179545-77-8; (prinomastat) 192329-42-3, 195008-93-6; (marimastat) 154039-60-8; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (doxorubicin)

23214-92-8, 25316-40-9; (n1 (1 carbamoyl 2,2 dimethylpropyl) 2 [3 (4 **chlorophenyl**)propyl] n4 hydroxybutanediamide) 162514-46-7; (gemcitabine) 103882-84-4; (4 dedimethylaminosancycline) 15866-90-7; (d 2163) 191537-76-5; (cgs 27023a) 169799-04-6; (temozolomide) 85622-93-1; (fluorouracil) 51-21-8; (cipemastat) 190648-49-8; (paclitaxel) 33069-62-4; (carboplatin) 41575-94-4; (ilomastat) 142880-36-2

CN (1) Bay 12 9566; (2) Bb 94; (3) Bb 2516; (4) Ag 3340; (5) Bms 275291; (6) Bms 275291; (7) Ro 32 3555; Cgs 27023a; Col 3; Ae 941; Gm 6001

CO (1) Bayer; (3) British Biotechnology; (4) Agouron; (5) Bristol; (6) Squibb; (7) Hoffmann La Roche

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ACCESSION NUMBER: 2002136784 EMBASE

TITLE: Selective requirement for CD40-CD154 in drug-induced type 1 versus type 2 responses to **trinitrophenyl** -ovalbumin.

AUTHOR: Nierkens S.; Van Helden P.; Bol M.; Bleumink R.; Van Kooten P.; Ramdien-Murli S.; Boon L.; Pieters R.

CORPORATE SOURCE: Dr. S. Nierkens, Department of Immunotoxicology, Institute for Risk Assessment Sci., Utrecht University, P.O. Box 80176, NL 3508 TD Utrecht, Netherlands. s.nierkens@iras.uu.nl

SOURCE: Journal of Immunology, (15 Apr 2002) Vol. 168, No. 8, pp. 3747-3754.
Refs: 49
ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20020502
Last Updated on STN: 20020502

ED Entered STN: 20020502
Last Updated on STN: 20020502

AB CD154 is transiently expressed by activated T cells and interacts with CD40 on B cells, dendritic cells, macrophages, and monocytes. This costimulatory receptor-ligand couple seems decisive in Ag-driven immune responses but may be differentially involved in type 1 vs type 2 responses. We studied the importance of CD40-CD154 in both responses using the reporter Ag popliteal lymph node assay in which selectively acting drugs generate clearly polarized type 1 (streptozotocin) or type 2 (D-penicillamine, **diphenylhydantoin**) responses to a constant coinjected Ag in the same mouse strain. Treatment of mice with anti-CD154 reduced characteristic immunological parameters in type 2 responses (B and CD4(+) T cell proliferation, IgG1 and IgE Abs, and IL-4 secretion) and only slightly affected the type 1 response (small decrease in IFN-γ production, influx of CD11c(+) and F4/80(+) cells, and prevention of architectural disruption of the lymph node, but no effect on IgG2a Ab and **TNF**-α secretion or B and CD4(+) T cell proliferation). The findings indicate that the CD40-CD154 costimulatory interaction is a prerequisite in drug-induced type 2 responses and is only marginally involved in type 1 responses. The observed expression patterns of CD80 and CD86 on different APC (B cells in type 2 and dendritic cells in type 1) may be responsible for this discrepancy.

CT Medical Descriptors:
*immune response
antigen expression
T lymphocyte activation

B lymphocyte
cell interaction
cytokine release
lymphocyte proliferation
cytokine production
lymph node
antigen presenting cell
dendritic cell
nonhuman
female
mouse
controlled study
animal cell
article
priority journal
Drug Descriptors:
*CD40 antigen: EC, endogenous compound
*CD40 ligand: EC, endogenous compound
***trinitrophenyl**
*ovalbumin
streptozocin
penicillamine
phenytoin
CD40 ligand monoclonal antibody
immunoglobulin G1: EC, endogenous compound
immunoglobulin E antibody: EC, endogenous compound
immunoglobulin G antibody: EC, endogenous compound
interleukin 4: EC, endogenous compound
gamma interferon: EC, endogenous compound
CD11 antigen: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
immunoglobulin G2a: EC, endogenous compound
RN (CD40 ligand) 226713-27-5; (ovalbumin) 77466-29-6; (streptozocin) 18883-66-4; (penicillamine) 2219-30-9, 52-67-5; (phenytoin) 57-41-0, 630-93-3; (gamma interferon) 82115-62-6

L51 ANSWER 28 OF 85 EMBASE
ACCESSION NUMBER: 2001299910 EMBASE
TITLE: Practical approaches to the **matrix metalloproteinase** inhibitor Trocade® (Ro 32-3555) and to the **TNF**-α **converting** enzyme inhibitor Ro 32-7315.
AUTHOR: Hilpert H.
CORPORATE SOURCE: H. Hilpert, F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, Non-Clin. Development-Process Res., Grenzacherstr. 124, CH-4070 Basel, Switzerland. hans.hilpert@roche.com
SOURCE: Tetrahedron, (3 Sep 2001) Vol. 57, No. 36, pp. 7675-7683. Refs: 16
ISSN: 0040-4020 CODEN: TETRAB
PUBLISHER IDENT.: S 0040-4020(01)00720-7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010913
Last Updated on STN: 20010913
ED Entered STN: 20010913

Last Updated on STN: 20010913
AB Stereoselective methods were found to efficiently prepare 2- and 3-substituted succinates with anti configuration. In the synthesis of Trocade® 1, the **hydantoinmethyl** residue was introduced by alkylation of the non-chelated potassium enolate 19 with the bromomethyl **hydantoin** 9 to give a 92:8 mixture favouring the 2,3-anti configurated succinate 18. The preparation of **TNF**-. **alpha. converting** enzyme (**TACE**) inhibitor 2 was accomplished by a highly stereoselective protonation of the dialkylated enolate 23 using CF(3)CONH(2) affording a 98:2 mixture in favour of the 2,3-anti configurated succinate 24.
CT Medical Descriptors:
drug structure
reaction analysis
stereochemistry
drug synthesis
alkylation
proton transport
article
priority journal
Drug Descriptors:
***matrix metalloproteinase inhibitor: DV, drug development**
***cipemastat: DV, drug development**
***tumor necrosis factor alpha: DV, drug development**
*ro 32 7315: DV, drug development
potassium derivative
hydantoin derivative
unclassified drug
RN (cipemastat) 190648-49-8
CN Trocade; Ro 32 3555; Ro 32 7315

L51 ANSWER 29 OF 85 EMBASE

ACCESSION NUMBER:	2001327458 EMBASE
TITLE:	Design and synthesis of **matrix metalloproteinase** inhibitors guided by molecular modeling. Picking the S(1) pocket using conformationally constrained inhibitors.
AUTHOR:	Hanessian S.; MacKay D.B.; Moitessier N.
CORPORATE SOURCE:	S. Hanessian, Department of Chemistry, Universite de Montreal, C. P. 6128, Succursale Centre-Ville, Montreal, Que. H3C 3J7, Canada. stephen.hanessian@umontreal.ca
SOURCE:	Journal of Medicinal Chemistry, (13 Sep 2001) Vol. 44, No. 19, pp. 3074-3082. Refs: 29 ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	030 Pharmacology 037 Drug Literature Index
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 20011018 Last Updated on STN: 20011018

ED Entered STN: 20011018
Last Updated on STN: 20011018
AB Conformationally constrained **MMP** inhibitors based on a D-proline scaffold were designed using AutoDock as a modeling program. Thus a family of D-proline **hydroxamic** acids, having differentiated

functionality at the site of binding to the S(1) pocket, was synthesized. Biological evaluation showed low nanomolar activity and modest selectivity toward different **MMP** subclasses, delineating the importance of binding to the S(1) pocket for both activity and selectivity.

CT Medical Descriptors:
drug design
drug synthesis
molecular model
drug conformation
binding site
enzyme inhibition
structure activity relation
IC 50
drug potency
hydrophobicity
article
Drug Descriptors:
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: PD, pharmacology**
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: DV, drug development
*hydroxamic acid derivative: PD, pharmacology
proline
matrix metalloproteinase
batimastat
cipemastat
cgs 27023a

RN (proline) 147-85-3, 7005-20-1; (batimastat) 130370-60-4, 130464-84-5; (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6

CO Bachem (Switzerland)

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ACCESSION NUMBER: 2001327457 EMBASE
TITLE: N-aryl sulfonyl homocysteine **hydroxamate** inhibitors of **matrix metalloproteinases** : Further probing of the S(1), S(1)', and S(2)' pockets.
AUTHOR: Hanessian S.; Moitessier N.; Gauchet C.; Viau M.
CORPORATE SOURCE: S. Hanessian, Department of Chemistry, Universite de Montreal, C.P. 6128, Succursale Centre-Ville, Montreal, Que. H3C 3J7, Canada. stephen.hanessian@umontreal.ca
SOURCE: Journal of Medicinal Chemistry, (13 Sep 2001) Vol. 44, No. 19, pp. 3066-3073.
Refs: 40
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20011018
Last Updated on STN: 20011018

ED Entered STN: 20011018
Last Updated on STN: 20011018

AB A series of N-arylsulfonyl S-alkyl homocysteine **hydroxamic** acids were synthesized with variations in three subsites corresponding to P(1), P(1)', and P(2)'. Enzyme assays with a variety of **MMPs** revealed activity at the low nanomolar level.

CT Medical Descriptors:
drug synthesis
enzyme assay
enzyme inhibition
enzyme activity
structure activity relation
chemical modification
molecular model
IC 50
article
Drug Descriptors:
*homocysteine
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: DV, drug development
*hydroxamic acid derivative: PD, pharmacology
*sulfonyl homocysteine hydroxamate derivative: AN, drug analysis
*sulfonyl homocysteine hydroxamate derivative: DV, drug development
*sulfonyl homocysteine hydroxamate derivative: PD, pharmacology
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: PD, pharmacology**
stromelysin
marimastat
cipemastat
cgs 27023a
prinomastat
gelatinase A
gelatinase B
interstitial collagenase
collagenase 3
unclassified drug
RN (homocysteine) 454-28-4, 6027-13-0; (stromelysin) 79955-99-0; (marimastat) 154039-60-8; (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6; (prinomastat) 192329-42-3, 195008-93-6; (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (collagenase 3) 175449-82-8
CN (1) Ro 32 3555; (2) Cgs 27023a; (3) Cgs 27023a; (4) Ag 3340
CO (1) Hoffmann La Roche; (2) Ciba Geigy; (3) Novartis; (4) Agouron; British Biotechnology

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ACCESSION NUMBER: 2001270928 EMBASE
TITLE: Biaryl ether **retrohydroxamates** as potent, long-lived, orally bioavailable **MMP** inhibitors.
AUTHOR: Michaelides M.R.; Dellaria J.F.; Gong J.; Holms J.H.; Bouska J.J.; Stacey J.; Wada C.K.; Heyman H.R.; Curtin M.L.; Guo Y.; Goodfellow C.L.; Elmore I.B.; Albert D.H.; Magoc T.J.; Marcotte P.A.; Morgan D.W.; Davidsen S.K.
CORPORATE SOURCE: M.R. Michaelides, Cancer Research Area, Abbott Laboratories, Dept. 47J, 100 Abbott Park Road, Abbott Park, IL 60064, United States. michael.michaelides@abbott.com
SOURCE: Bioorganic and Medicinal Chemistry Letters, (18 Jun 2001) Vol. 11, No. 12, pp. 1553-1556.
Refs: 10
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(01)00031-2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology

037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010816
Last Updated on STN: 20010816
ED Entered STN: 20010816
Last Updated on STN: 20010816
AB A novel series of biaryl ether reverse **hydroxamate MMP** inhibitors has been developed. These compounds are potent **MMP**-2 inhibitors with limited activity against **MMP**-1. Select members of this series exhibit excellent pharmacokinetic properties with long elimination half-lives (7 h) and high oral bioavailability (100%).

CT Medical Descriptors:
drug potency
drug mechanism
drug half life
drug bioavailability
drug structure
drug synthesis
reaction analysis
IC 50
enzyme inhibition
stoichiometry
enzyme activity
structure activity relation
monkey
antineoplastic activity
human
nonhuman
rat
clinical trial
animal experiment
controlled study
article
Drug Descriptors:
*hydroxamic acid derivative: CT, clinical trial
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: DV, drug development
*hydroxamic acid derivative: PK, pharmacokinetics
*hydroxamic acid derivative: PD, pharmacology
*hydroxamic acid derivative: IV, intravenous drug administration
*hydroxamic acid derivative: PO, oral drug administration
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: PK, pharmacokinetics**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: IV, intravenous drug administration**
***matrix metalloproteinase inhibitor: PO, oral drug administration**
*ether retrohydroxamate derivative: CT, clinical trial
*ether retrohydroxamate derivative: AN, drug analysis
*ether retrohydroxamate derivative: DV, drug development
*ether retrohydroxamate derivative: PK, pharmacokinetics
*ether retrohydroxamate derivative: PD, pharmacology
*ether retrohydroxamate derivative: IV, intravenous drug administration
*ether retrohydroxamate derivative: PO, oral drug administration
ether hydroxamate derivative: CT, clinical trial
ether hydroxamate derivative: AN, drug analysis

ether hydroxamate derivative: DV, drug development
ether hydroxamate derivative: PK, pharmacokinetics
ether hydroxamate derivative: PD, pharmacology
ether hydroxamate derivative: PO, oral drug administration
hydantoin derivative: CT, clinical trial
hydantoin derivative: CM, drug comparison
hydantoin derivative: DV, drug development
hydantoin derivative: PK, pharmacokinetics
hydantoin derivative: PD, pharmacology
hydantoin derivative: PO, oral drug administration
antineoplastic agent: CT, clinical trial
antineoplastic agent: AN, drug analysis
antineoplastic agent: CM, drug comparison
antineoplastic agent: DV, drug development
antineoplastic agent: PK, pharmacokinetics
antineoplastic agent: PD, pharmacology
antineoplastic agent: IV, intravenous drug administration
antineoplastic agent: PO, oral drug administration
acetic acid derivative: CM, drug comparison
acetic acid derivative: PK, pharmacokinetics
acetic acid derivative: PD, pharmacology
acetic acid derivative: IV, intravenous drug administration
succinimide derivative: CM, drug comparison
succinimide derivative: PK, pharmacokinetics
succinimide derivative: PD, pharmacology
succinimide derivative: IV, intravenous drug administration
phthalimide derivative: CM, drug comparison
phthalimide derivative: PK, pharmacokinetics
phthalimide derivative: PD, pharmacology
phthalimide derivative: IV, intravenous drug administration
pyridazinone derivative: CM, drug comparison
pyridazinone derivative: PK, pharmacokinetics
pyridazinone derivative: PD, pharmacology
pyridazinone derivative: IV, intravenous drug administration
cipemastat: CT, clinical trial
cipemastat: CM, drug comparison
cipemastat: DV, drug development
cipemastat: PK, pharmacokinetics
cipemastat: PD, pharmacology
cipemastat: PO, oral drug administration
d 2163: CT, clinical trial
d 2163: CM, drug comparison
d 2163: DV, drug development
d 2163: PK, pharmacokinetics
d 2163: PD, pharmacology
d 2163: PO, oral drug administration
drug metabolite
unclassified drug
RN (cipemastat) 190648-49-8; (d 2163) 191537-76-5
CN D 2163; Ro 323555

L51 ANSWER 32 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001068613 EMBASE
TITLE: Novel spirohydantoins of D-allose and D-ribose derived from glyco-α-aminonitriles.
AUTHOR: Postel D.; Nguyen Van Nhien A.; Villa P.; Ronco G.
CORPORATE SOURCE: D. Postel, Laboratoire des Glucides, Universite de Picardie-Jules Verne, 33 rue Saint Leu, 80039 Amiens, France. denis.postel@sc.u-picardie.fr

SOURCE: Tetrahedron Letters, (19 Feb 2001) Vol. 42, No. 8, pp. 1499-1502.
Refs: 12
ISSN: 0040-4039 CODEN: TELEAY
PUBLISHER IDENT.: S 0040-4039(00)02294-2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010316
Last Updated on STN: 20010316
ED Entered STN: 20010316
Last Updated on STN: 20010316
AB The synthesis of 3-**spirohydantoin** derivatives of D-allose and D-ribose is reported. The key step is the stereoselective **conversion** of glyco-α -aminonitriles from ulose derivatives of D-glucose and D-xylose using titanium(IV) isopropoxide as a mild and efficient catalyst. Cyclisation of the glyco-α-aminonitriles give the target **spirohydantoins.** .COPYRGT. 2001 Elsevier Science Ltd.
CT Medical Descriptors:
*cyclization
synthesis
catalyst
precursor
oxidation
reaction analysis
decarboxylation
article
Drug Descriptors:
*allose
*ribose
*nitrile
*glyco alpha aminonitrile
***hydantoin derivative**
*3 spirohydantoin
glucose
xylose
titanium derivative
titanium 4 isopropoxide
unclassified drug
RN (allose) 6038-51-3; (ribose) 34466-20-1, 50-69-1, 93781-19-2; (glucose) 50-99-7, 84778-64-3; (xylose) 25990-60-7, 58-86-6

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ACCESSION NUMBER: 2001202807 EMBASE
TITLE: Induction of tumour cell apoptosis by **matrix metalloproteinase** inhibitors: New tricks from a (not so) old drug.
AUTHOR: Mitsiades N.; Poulaki V.; Mitsiades C.S.; Anderson K.C.
CORPORATE SOURCE: K.C. Anderson, Department of Adult Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, United States
SOURCE: Expert Opinion on Investigational Drugs, (2001) Vol. 10, No. 6, pp. 1075-1084.
Refs: 86
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010710
Last Updated on STN: 20010710

ED Entered STN: 20010710
Last Updated on STN: 20010710

AB **Matrix metalloproteinases** (**MMPs**) regulate the turnover of extracellular matrix (ECM) components and play an important role in embryo development, morphogenesis and tissue remodelling, as well as in tumour invasion and metastasis. Synthetic **MMP** inhibitors (MMPIs) were designed to prevent tumour cell-induced changes in ECM and thereby achieve antitumour activity. Several MMPIs have entered clinical trials but the preliminary results did not meet the expectations. Recent evidence suggests that **MMPs** may have more diverse roles than originally believed, influencing angiogenesis, cytokine secretion, as well as tumour cell growth and survival. In particular, synthetic MMPIs may directly induce apoptosis of cancer cells via their inhibitory effect on the shedding of Fas Ligand (FasL), a transmembrane member of the **TNF** superfamily that kills susceptible cells through its receptor, Fas. Several types of cancers have been shown to express FasL and to shed it from their surface as a soluble form, which is significantly less potent in promoting apoptosis. **MMP**-7 was recently reported to catalyse this process. Conversely, inhibition of FasL-shedding by a synthetic MMPI results in apoptosis of Fas-sensitive cancer cells. More importantly, DNA-damaging anticancer agents, such as adriamycin, kill cancer cells, at least in part, by upregulating FasL. By inhibiting the proteolytic cleavage of FasL, MMPIs can potentiate the killing effect of traditional chemotherapeutic drugs. These studies therefore demonstrate a direct link between DNA-damaging chemotherapeutic drugs, the apoptosis-inducing Fas/FasL system and the proteolytic activity of **MMPs** and have important therapeutic implications. For example, the proteolytic activity of **MMP**-7, which is broadly expressed in primary and especially metastatic human malignancies, may contribute to tumour resistance to cytotoxic agents; targeting and inactivating **MMP**-7 may, therefore, enhance the efficacy of conventional cancer chemotherapy.

CT Medical Descriptors:
tumor cell
apoptosis
extracellular matrix
embryo development
morphogenesis
cancer invasion
metastasis
drug design
antineoplastic activity
angiogenesis
cytokine release
tumor growth
cell survival
cancer cell
inhibition kinetics
protein family
cell killing

drug potency
enzyme mechanism
DNA damage
protein degradation
drug potentiation
protein expression
malignant neoplastic disease: DT, drug therapy
tumor resistance
protein targeting
enzyme inactivation
drug efficacy
drug bioavailability
drug tolerability
bone marrow suppression: SI, side effect
immune deficiency: SI, side effect
gastrointestinal disease: SI, side effect
volunteer
musculoskeletal disease: SI, side effect
drug selectivity
advanced cancer: DT, drug therapy
in vitro study
human
nonhuman
mouse
human experiment
normal human
clinical trial
phase 1 clinical trial
phase 3 clinical trial
animal experiment
animal model
controlled study
human cell
animal cell
review
Drug Descriptors:
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: IT, drug interaction**
***matrix metalloproteinase inhibitor: DT, drug therapy**
***matrix metalloproteinase inhibitor: PD, pharmacology**
matrix metalloproteinase: EC, endogenous compound
cytokine: EC, endogenous compound
FAS ligand: EC, endogenous compound
membrane protein: EC, endogenous compound
tumor necrosis factor: EC, endogenous compound
Fas antigen: EC, endogenous compound
matrilysin: EC, endogenous compound
antineoplastic agent: IT, drug interaction
antineoplastic agent: DT, drug therapy
antineoplastic agent: PD, pharmacology
doxorubicin: DT, drug therapy
doxorubicin: PD, pharmacology
cytotoxic agent: PD, pharmacology
interstitial collagenase: EC, endogenous compound
batimastat: CT, clinical trial
batimastat: DV, drug development
batimastat: DT, drug therapy
batimastat: PK, pharmacokinetics
batimastat: PD, pharmacology

marimastat: CT, clinical trial
marimastat: DV, drug development
marimastat: DT, drug therapy
marimastat: PD, pharmacology
prinomastat: AE, adverse drug reaction
prinomastat: CT, clinical trial
prinomastat: DV, drug development
prinomastat: DT, drug therapy
prinomastat: PD, pharmacology
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: AE, adverse drug reaction
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: CT, clinical trial
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: DV, drug development
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: DT, drug therapy
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: PD, pharmacology
cgs 27023a: AE, adverse drug reaction
cgs 27023a: CT, clinical trial
cgs 27023a: DV, drug development
cgs 27023a: DT, drug therapy
cgs 27023a: PD, pharmacology
d 2163: AE, adverse drug reaction
d 2163: CT, clinical trial
d 2163: DV, drug development
d 2163: DT, drug therapy
d 2163: PD, pharmacology
4 dedimethylaminosancycline: AE, adverse drug reaction
4 dedimethylaminosancycline: CT, clinical trial
4 dedimethylaminosancycline: DV, drug development
4 dedimethylaminosancycline: DT, drug therapy
4 dedimethylaminosancycline: PD, pharmacology
nerve growth factor receptor: EC, endogenous compound
caspase 8: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
tumor necrosis factor alpha converting enzyme: PD, pharmacology
solimastat: CT, clinical trial
solimastat: DV, drug development
solimastat: DT, drug therapy
solimastat: PD, pharmacology
cipemastat: CT, clinical trial
cipemastat: DV, drug development
cipemastat: DT, drug therapy

CT Drug Descriptors:

cipemastat: PD, pharmacology
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CT, clinical trial
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: DV, drug development
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: DT, drug therapy
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: PD, pharmacology
gelatinase A: EC, endogenous compound
stromelysin: EC, endogenous compound
gelatinase B: EC, endogenous compound
unindexed drug

RN (matrilysin) 141256-52-2; (doxorubicin) 23214-92-8, 25316-40-9;

(batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (4 (4' **chlorobiphenyl** 4 yl) 4 oxo 2 (**phenylthiomethyl**)butyric acid) 179545-76-7, 179545-77-8; (cgs 27023a) 169799-04-6; (d 2163) 191537-76-5; (4 dedimethylaminosancycline) 15866-90-7; (**tumor necrosis** factor **alpha converting** enzyme) 151769-16-3; (cipemastat) 190648-49-8; (4 [[[4 (4 chlorophenoxy)**phenyl**]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (gelatinase A) 146480-35-5; (stromelysin) 79955-99-0; (gelatinase B) 146480-36-6

CN (1) Ag 3340; (2) Ag 3340; (3) Bay 129566; (4) Cgs 27023a; (5) Bms 275291; (6) Bms 275291; (7) Metastat; Bb 94; Bb 2516; Ro 32 3555; Rs 130830

CO (1) Agouron; (2) Pfizer; (3) Bayer; (4) Novartis; (5) Celltech; (6) Bms; (7) Collagenex

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ACCESSION NUMBER: 2002038795 EMBASE
TITLE: Metalloproteases and inhibitors in arthritic diseases.
AUTHOR: Martel-Pelletier J.; Welsch D.J.; Pelletier J.-P.
CORPORATE SOURCE: Prof. Dr. J. Martel-Pelletier, Osteoarthritis Research Unit, Hopital Notre-Dame, Ctr. Hosp. de l'Univ. de Montreal, 1560 rue Sherbrooke Est, Montreal, Que., Canada
SOURCE: Bailliere's Best Practice and Research in Clinical Rheumatology, (2001) Vol. 15, No. 5, pp. 805-829.
Refs: 65
ISSN: 1521-6942 CODEN: BBPRFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
030 Pharmacology
038 Adverse Reactions Titles
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020207
Last Updated on STN: 20020207

ED Entered STN: 20020207
Last Updated on STN: 20020207

AB Controlling degradation of the extracellular matrix is crucial in arthritic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA), as conventional treatments do not positively affect the structural properties of the articular tissues. Metalloproteases, a family of zinc-dependent enzymes, and more specifically the **matrix metalloproteases** (**MMPs**), play a premier role in joint articular tissue degeneration. Additional enzymes of the metalloprotease family, such as the membrane-type metalloproteases (MT-**MMPs**) and the adamalysins that include the ADAMs and the ADAMTS families, have also been found to be involved in these disease processes. At present, therapeutic intervention based on the inhibition of metalloproteases, and more particularly of the **MMPs**, is under intensive investigation, and several **MMP** inhibitors are in clinical development. Currently, **MMP** inhibitors are exemplified by several chemical classes: **hydroxamic** acids, carboxylic acids and thiols. One key issue in the clinical development of **MMP** inhibitors relates to whether broad-spectrum inhibitors active against a range of different enzymes or selective inhibitors targeted against a single enzyme or particular subset of the **MMPs** represents the optimal strategy.

In this chapter, we address the different metalloprotease enzymes and sub-families and their implication in arthritic diseases. Furthermore, we assess physiological and chemical metalloprotease inhibitors, and for the latter, the current inhibitory classes of compounds being studied.

CT Medical Descriptors:
*arthritis: DT, drug therapy
*arthritis: ET, etiology
*arthritis: DI, diagnosis
human
clinical trial
nonhuman
degradation
extracellular matrix
osteoarthritis: DT, drug therapy
osteoarthritis: ET, etiology
osteoarthritis: DI, diagnosis
rheumatoid arthritis: DT, drug therapy
rheumatoid arthritis: ET, etiology
rheumatoid arthritis: DI, diagnosis
tissue degeneration: ET, etiology
enzyme inhibition
physiology
enzyme synthesis
enzyme activation
drug bioavailability
drug identification
structure activity relation
musculoskeletal disease: SI, side effect
drug synthesis
drug design
dose response
rash: SI, side effect
nuclear magnetic resonance imaging
articular cartilage
transcription regulation
review
priority journal
Drug Descriptors:
*metalloproteinase: EC, endogenous compound
*metalloproteinase inhibitor: PD, pharmacology
*metalloproteinase inhibitor: DT, drug therapy
*metalloproteinase inhibitor: DV, drug development
*metalloproteinase inhibitor: AN, drug analysis
*metalloproteinase inhibitor: PK, pharmacokinetics
*metalloproteinase inhibitor: PO, oral drug administration
*metalloproteinase inhibitor: AE, adverse drug reaction
*metalloproteinase inhibitor: DO, drug dose
*metalloproteinase inhibitor: CT, clinical trial
*metalloproteinase inhibitor: CM, drug comparison
*metalloproteinase inhibitor: IV, intravenous drug administration
zinc: EC, endogenous compound
matrix metalloproteinase: EC, endogenous compound
matrix metalloproteinase 14: EC, endogenous compound
hydroxamic acid: PD, pharmacology
carboxylic acid: PD, pharmacology
thiol derivative: PD, pharmacology
thiol derivative: CM, drug comparison
tissue inhibitor of metalloproteinase: PD, pharmacology
tissue inhibitor of metalloproteinase: DT, drug therapy
tissue inhibitor of metalloproteinase: PO, oral drug administration

tissue inhibitor of metalloproteinase: PK, pharmacokinetics
tetracycline derivative: PD, pharmacology
tetracycline derivative: DT, drug therapy
tetracycline derivative: IV, intravenous drug administration
antibiotic agent: PD, pharmacology
antibiotic agent: DT, drug therapy
antibiotic agent: CT, clinical trial
antibiotic agent: IV, intravenous drug administration
bryostatin: PD, pharmacology
bisphosphonic acid derivative: PD, pharmacology
doxycycline: PD, pharmacology
doxycycline: IV, intravenous drug administration
doxycycline: DT, drug therapy
tumor necrosis factor alpha converting enzyme: EC, endogenous compound
cyclooxygenase 2 inhibitor: DT, drug therapy
cyclooxygenase 2 inhibitor: PD, pharmacology
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PD, pharmacology
sc 44463: AN, drug analysis
sc 44463: PD, pharmacology
sc 44463: PK, pharmacokinetics
sc 44463: PO, oral drug administration
sc 44463: AE, adverse drug reaction
sc 44463: DT, drug therapy
batimastat: AN, drug analysis
batimastat: PD, pharmacology
batimastat: PK, pharmacokinetics
batimastat: PO, oral drug administration
batimastat: AE, adverse drug reaction
batimastat: DT, drug therapy
ilomastat: AN, drug analysis
ilomastat: PD, pharmacology
ilomastat: PK, pharmacokinetics
ilomastat: PO, oral drug administration
ilomastat: AE, adverse drug reaction
ilomastat: DT, drug therapy
marimastat: PD, pharmacology
marimastat: PO, oral drug administration
marimastat: PK, pharmacokinetics
marimastat: AE, adverse drug reaction
marimastat: AN, drug analysis
marimastat: DO, drug dose
marimastat: CT, clinical trial
marimastat: DT, drug therapy
prinomastat: PD, pharmacology
prinomastat: PO, oral drug administration
prinomastat: AN, drug analysis
prinomastat: DT, drug therapy
d 2163: PD, pharmacology
d 2163: DT, drug therapy
cipemastat: PD, pharmacology
cipemastat: CT, clinical trial
cipemastat: DT, drug therapy
cgs 27023a: PD, pharmacology
cgs 27023a: PO, oral drug administration
cgs 27023a: AN, drug analysis
cgs 27023a: DT, drug therapy
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: PD, pharmacology

4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CT, clinical trial
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CB, drug combination
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: DT, drug therapy
bay 12 9556: PD, pharmacology

CT Drug Descriptors:
bay 12 9556: DT, drug therapy
rs 102481: PD, pharmacology
rs 102481: DT, drug therapy
minocycline: PD, pharmacology
minocycline: DT, drug therapy
unindexed drug
unclassified drug

RN (metalloproteinase) 81669-70-7; (zinc) 7440-66-6; (thiol derivative) 13940-21-1; (tissue inhibitor of metalloproteinase) 97837-28-0; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (**tumor necrosis** factor **alpha converting** enzyme) 151769-16-3; (batimastat) 130370-60-4, 130464-84-5; (ilomastat) 142880-36-2; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (d 2163) 191537-76-5; (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6; (4 [[[4 (4 chlorophenoxy)**phenyl**]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (minocycline) 10118-90-8, 11006-27-2, 13614-98-7

CN (1) Trocade; (2) Ro 32 3555; Bb 94; Gm 6001; Sc 44463; Bb 2516; Ag 3340; D 2163; Bms 275291; Cgs 27023a; Rs 102481; Bay 12 9556; Rs 130830

CO (2) Hoffmann La Roche

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ACCESSION NUMBER:	2001050554 EMBASE
TITLE:	General synthesis of α-substituted 3-bisaryloxy propionic acid derivatives as specific **MMP** inhibitors.
AUTHOR:	Chollet A.-M.; Le Diguarher T.; Murray L.; Bertrand M.; Tucker G.C.; Sabatini M.; Pierre A.; Atassi G.; Bonnet J.; Casara P.
CORPORATE SOURCE:	P. Casara, Institut de Recherches Servier, 125 chemin de Ronde, 78290 Croissy sur Seine, France. patrick.casara@fr.netgrs.com
SOURCE:	Bioorganic and Medicinal Chemistry Letters, (12 Feb 2001) Vol. 11, No. 3, pp. 295-299. Refs: 45 ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.:	S 0960-894X(00)00646-6
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	030 Pharmacology 037 Drug Literature Index
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 20010322 Last Updated on STN: 20010322

ED Entered STN: 20010322
Last Updated on STN: 20010322

AB Modulations of α and aryl substitutions on 3-aryloxy propionic acid **hydroxamates** led to novel and potent inhibitors of **MMP** -2,3,9 and 13, and selectivity versus **MMP**-1. .COPYRGT. 2001 Elsevier Science Ltd.

CT Medical Descriptors:
*drug synthesis
enzyme inhibition
drug structure
human
controlled study
human cell
article
Drug Descriptors:
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: DV, drug development**
*propionic acid derivative: AN, drug analysis
*propionic acid derivative: DV, drug development
gelatinase A
gelatinase B
matrix metalloproteinase
interstitial collagenase
cipemastat
marimastat
prinomastat
cgs 27023a
RN (gelatinase A) 146480-35-5; (gelatinase B) 146480-36-6; (cipemastat) 190648-49-8; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (cgs 27023a) 169799-04-6
CN Trocade; Marimastat; Prinomastat; Cgs 27023a

L51 ANSWER 36 OF 85 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001009796 EMBASE
TITLE: Sulfone reverse **hydroxamates** as **matrix metalloproteinase** inhibitors.
SOURCE: Expert Opinion on Therapeutic Patents, (2001) Vol. 11, No. 1, pp. 133-143.
Refs: 30
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010119
Last Updated on STN: 20010119
ED Entered STN: 20010119
Last Updated on STN: 20010119
AB Abbott has disclosed **matrix metalloproteinase** inhibitors (MMPIs) characterised by N-formyl-N-hydroxyamino as the zinc ligand, (4-substituted)**phenylsulfonyl** as the P1' group fitting the primary specificity pocket of the enzymes and three different spacers (-C-C-C-, -C-C-NR-, -C-C-) connecting these structural elements. As such, the Abbott compounds can be regarded as reverse **hydroxamate** analogues of the well known classes of γ-sulfone, sulfonamide and β-sulfone **hydroxamate** MMPIs. Within the β-sulfones, a five-membered saturated heterocyclic ring appended at C-1, especially 1,3-dioxolane, identifies a structural subset claimed as having a unique combination of potency, pharmacokinetics and fewer side effects. A specific compound is singled out, (1S) -1-[(4S) -2, 2- dimethyl-1,3

-dioxolan -4-yl] -2-[[4 -[4-(trifluoromethoxy)phenoxy] -phenyl]sulfonyl] ethyl(N-hydroxy)formamide. Potent inhibition of **MMP**-2 (gelatinase A) is documented, especially among the β-sulfones. These compounds are stated to have utility for the treatment of diseases involving tissue degenerative processes, including rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration and tumour growth and metastasis.

CT Medical Descriptors:
patent
drug structure
drug potency
enzyme inhibition
tissue degeneration
rheumatoid arthritis
osteoarthritis
osteoporosis
periodontitis
gingivitis
cornea ulcer
skin ulcer
stomach ulcer
tumor growth
metastasis
drug activity
IC 50
drug bioavailability
drug synthesis
chemical reaction
drug half life
structure activity relation
human
nonhuman
mouse
rat
clinical trial
animal experiment
animal model
controlled study
article
Drug Descriptors:
***matrix metalloproteinase inhibitor: CT, clinical trial**
***matrix metalloproteinase inhibitor: AN, drug analysis**
***matrix metalloproteinase inhibitor: CM, drug comparison**
***matrix metalloproteinase inhibitor: DV, drug development**
***matrix metalloproteinase inhibitor: PK, pharmacokinetics**
***matrix metalloproteinase inhibitor: PD, pharmacology**
***matrix metalloproteinase inhibitor: PO, oral drug administration**
***matrix metalloproteinase inhibitor: SC, subcutaneous drug administration**
*hydroxamic acid derivative: CT, clinical trial
*hydroxamic acid derivative: AN, drug analysis
*hydroxamic acid derivative: CM, drug comparison
*hydroxamic acid derivative: DV, drug development
*hydroxamic acid derivative: PK, pharmacokinetics
*hydroxamic acid derivative: PD, pharmacology
*hydroxamic acid derivative: PO, oral drug administration
*hydroxamic acid derivative: SC, subcutaneous drug administration
*sulfone derivative: CT, clinical trial
*sulfone derivative: AN, drug analysis
*sulfone derivative: CM, drug comparison

*sulfone derivative: DV, drug development
*sulfone derivative: PK, pharmacokinetics
*sulfone derivative: PD, pharmacology
*sulfone derivative: PO, oral drug administration
*sulfone derivative: SC, subcutaneous drug administration
zinc
ligand
sulfonamide
1,3 dioxolane
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4 (trifluoromethoxy)phenoxylphenyl]sulfonyl]ethyl n hydroxyformamide: AN, drug analysis
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4 (trifluoromethoxy)phenoxylphenyl]sulfonyl]ethyl n hydroxyformamide: DV, drug development
1 (2,2 dimethyl 1,3 dioxolan 4 yl) 2 [4 [4 (trifluoromethoxy)phenoxylphenyl]sulfonyl]ethyl n hydroxyformamide: PD, pharmacology
gelatinase A: EC, endogenous compound
batimastat: CT, clinical trial
batimastat: AN, drug analysis
batimastat: PD, pharmacology
marimastat: CT, clinical trial
marimastat: AN, drug analysis
marimastat: CM, drug comparison
marimastat: PK, pharmacokinetics
marimastat: PD, pharmacology
cipemastat: CT, clinical trial
cipemastat: AN, drug analysis
cipemastat: PD, pharmacology
cgs 27023a: CT, clinical trial
cgs 27023a: AN, drug analysis
cgs 27023a: CM, drug comparison
cgs 27023a: PD, pharmacology
prinomastat: CT, clinical trial
prinomastat: AN, drug analysis
prinomastat: CM, drug comparison
prinomastat: PD, pharmacology
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: CT, clinical trial
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: AN, drug analysis
4 (4' chlorobiphenyl 4 yl) 4 oxo 2 (phenylthiomethyl)butyric acid: PD, pharmacology
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: CT, clinical trial
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: AN, drug analysis
4 [[[4 (4 chlorophenoxy)phenyl]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid: PD, pharmacology
d 2163: CT, clinical trial
d 2163: AN, drug analysis
d 2163: PD, pharmacology
gw 3333: AN, drug analysis
gw 3333: PK, pharmacokinetics
gw 3333: PD, pharmacology
gw 3333: PO, oral drug administration
ag 3151: AN, drug analysis
ag 3151: PD, pharmacology
interstitial collagenase: EC, endogenous compound

stromelysin: EC, endogenous compound
gelatinase B: EC, endogenous compound
n [3 (3 phenoxyphenyl)allyl]acetohydroxamic acid: AN, drug analysis
bw 218c: AN, drug analysis
tumor necrosis factor alpha converting enzyme: EC, endogenous compound
gi 179: CM, drug comparison
gi 179: PK, pharmacokinetics
gi 179: PD, pharmacology
gi 179: SC, subcutaneous drug administration
gi 184: CM, drug comparison
gi 184: PK, pharmacokinetics
gi 184: PD, pharmacology
unclassified drug
ro 1130830

RN (zinc) 7440-66-6; (1,3 dioxolane) 646-06-0; (gelatinase A) 146480-35-5; (batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8; (cipemastat) 190648-49-8; (cgs 27023a) 169799-04-6; (prinomastat) 192329-42-3, 195008-93-6; (4 (4' **chlorobiphenyl** 4 yl) 4 oxo 2 (**phenylthiomethyl**)butyric acid) 179545-76-7, 179545-77-8; (4 [[[4 (4 chlorophenoxy)**phenyl**]sulfonyl]methyl]tetrahydro 2h pyran 4 carbohydroxamic acid) 193022-04-7; (d 2163) 191537-76-5; (stromelysin) 79955-99-0; (gelatinase B) 146480-36-6; (n [3 (3 **phenoxyphenyl**)allyl]acetohydroxamic acid) 106328-57-8; (**tumor necrosis** factor **alpha converting** enzyme) 151769-16-3

CN (1) Ro 323555; (2) Cgs 27023a; (3) Ag 3340; (4) Bay 129566; (5) Ro 1130830; (6) Bms 275291; (7) D 2163; (8) Ag 3151; Gw 3333; Bw 218c; Gi 179; Gi 184

CO (2) Novartis; (4) Bayer; (5) Hoffmann La Roche; (7) Chiroscience; (8) Agouron; British Biotechnology; Abbott; Pharmacia; Celltech; Syntex; Glaxo Wellcome; Astra Zeneca; Burroughs Wellcome; Darwin Discovery

L51 ANSWER 37 OF 85 EMBASE

ACCESSION NUMBER: 93105406 EMBASE
DOCUMENT NUMBER: 1993105406
TITLE: Cell transforming and oncogenic activity of 2,3,7,8 - tetrachloro - and 2,3,7,8 tetrabromodibenzo-p-dioxin.
AUTHOR: Massa T.; Esmaeili A.; Fortmeyer H.; Schlatterer B.; Hagenmaier H.; Chandra P.
CORPORATE SOURCE: Molecular Biology (ZBC), University Medical School, Stern-Kai 7,D-6000 Frankfurt 71, Germany
SOURCE: Anticancer Research, (1992) Vol. 12, No. 6 B, pp. 2053-2060.
ISSN: 0250-7005 CODEN: ANTRD4
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930516
Last Updated on STN: 930516

ED Entered STN: 930516
Last Updated on STN: 930516

AB We have developed a host-mediated assay system for detection of the transforming activity of chemical carcinogens on peritoneal macrophages, directly, as well as indirectly acting carcinogenic substances

administered intraperitoneally to NMRI mice could be examined in this way. Resident macrophages were recovered by peritoneal lavage from treated and untreated mice and cultured in soft agar. After 5-6 days normal and transformed cells could be distinguished. Statistical analysis comparing cells from 2, 3, 7, 8-tetrachlorodibenzo-dioxin (TCDD)-treated animals with those from control mice proved that the test is positive at least on a significance level of 5%, using the t-test. TCDD revealed a cell-transforming potential that showed a dose-dependent response in this host-mediated assay. The co-carcinogenic activity of TCDD was established in experiments with **diphenylhydantoin.** Low doses of **diphenylhydantoin** which did not exhibit any transforming potential in our system gained a high oncogenic potential by the simultaneous administration of low doses of TCDD, which also had no transforming activity. We have compared the cell transforming potential of TCDD with its bromo analog TBrDD. The cell transforming potential of TCDD is 7 times that of TBrDD. We have succeeded in establishing a permanent cell lined from mice treated with TBrDD. The oncogenicity of this cell line was tested in athymic nu/nu mice. Animals treated subcutaneously with these cells (1 x 106 cells) developed tumors at the injection site. Using monospecific antibodies to **tumor necrosis** factor a (**TNF**-α), we have found that TCDD stimulates the secretion of **TNF**-α. The experimental data reported here lead to the conclusion that TCDD has a carcinogenic as well as a co-carcinogenic activity and has the property to induce **TNF**-α.

CT Medical Descriptors:
*carcinogenicity
*cell transformation
animal cell
animal experiment
animal model
article
bioassay
cell line
chemical carcinogenesis
controlled study
immunoassay
lavage
mouse
nonhuman
peritoneum macrophage
priority journal
statistical analysis
Drug Descriptors:
*dioxin: TO, drug toxicity
2,3,7,8 tetrachlorodibenzo para dioxin: TO, drug toxicity
carcinogen: TO, drug toxicity
phenytoin: TO, drug toxicity

RN (2,3,7,8 tetrachlorodibenzo para dioxin) 1746-01-6; (phenytoin) 57-41-0, 630-93-3

L51 ANSWER 38 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:364644 BIOSIS
DOCUMENT NUMBER: PREV200510145190
TITLE: Non-**hydroxamate** 5-**phenylpyrimidine** -2,4,6-trione derivatives as selective inhibitors of **tumor necrosis** factor-**alpha converting** enzyme.
AUTHOR(S): Duan, James J.-W. [Reprint Author]; Lu, Zhonghui; Wasserman, Zelda R.; Liu, Rui-Qin; Covington, Maryanne B.;

Decicco, Carl P.
CORPORATE SOURCE: Bristol Myers Squibb Pharmaceut Res Inst, Princeton, NJ 08543 USA
james.duan@bms.com
SOURCE: Bioorganic & Medicinal Chemistry Letters, (JUN 15 2005) Vol. 15, No. 12, pp. 2970-2973.
CODEN: BMCLE8. ISSN: 0960-894X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Sep 2005
Last Updated on STN: 14 Sep 2005
ED Entered STN: 14 Sep 2005
Last Updated on STN: 14 Sep 2005
AB New inhibitors of **tumor necrosis** factor-a converting enzyme (**TACE**) were discovered with a pyrimidine-2,4,6-trione in place of the commonly used **hydroxamic** acid. These non-**hydroxamate TACE** inhibitors were developed by incorporating a 4-(2methyl-4-quinolinylmethoxy)phenyl group, an optimized **TACE** selective P1' group. Several leads were identified with IC50 values around 100 nM in a porcine **TACE** assay and selective over **MMP**-1, -2, -9, -13, and aggrecanase. (c) 2005 Elsevier Ltd. All rights reserved.
CC Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Immunological processes and allergy 22018
Immunology - General and methods 34502
IT Major Concepts
Pharmacology; Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis)
IT Chemicals & Biochemicals
matrix metalloproteinase-2 [MMP-2] [EC 3.4.24.24]; **matrix metalloproteinase-9 [MMP-9] [EC 3.4.24.35]**; **matrix metalloproteinase-1 [MMP-1] [EC 3.4.24.3]**; **matrix metalloproteinase-13 [MMP-13]**; aggrecanase; **tumor necrosis factor-alpha-converting enzyme [TACE]**; 5-phenylpyrimidine-2,4,6-trione derivatives: enzyme inhibitor-drug, immunosuppressant-drug, immunologic-drug
ORGN Classifier
Suidae 85740
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
porcine (common)
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
RN 146480-35-5 (**matrix metalloproteinase**-2)
146480-35-5 (**MMP**-2)
146480-35-5 (EC 3.4.24.24)
146480-36-6 (**matrix metalloproteinase**-9)
146480-36-6 (**MMP**-9)
146480-36-6 (EC 3.4.24.35)
9001-12-1 (**matrix metalloproteinase**-1)
9001-12-1 (**MMP**-1)
9001-12-1 (EC 3.4.24.3)
175449-82-8 (**matrix metalloproteinase**-13)
175449-82-8 (**MMP**-13)
147172-61-0 (aggrecanase)

151769-16-3 (**tumor necrosis** factor-**alpha-converting** enzyme)
151769-16-3 (**TACE**)

L51 ANSWER 39 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:95815 BIOSIS
DOCUMENT NUMBER: PREV200500095816
TITLE: Synthesis and structure-activity relationships of 4-alkynyloxy **phenyl** sulfanyl, sulfinyl, and sulfonyl alkyl **hydroxamates** as **tumor necrosis** factor-**alpha converting** enzyme and **matrix metalloproteinase** inhibitors.
AUTHOR(S): Venkatesan, Aranapakam M. [Reprint Author]; Davis, Jamie M.; Grosu, George T.; Baker, Jannie; Zask, Arie; Levin, Jeremy I.; Ellingboe, John; Skotnicki, Jerauld S.; DiJoseph, John F.; Sung, Amy; Jin, Guixian; Xu, Weixin; McCarthy, Diane Joseph; Barone, Dauphine
CORPORATE SOURCE: Wyeth Ayerst Res, 401 N Middletown Rd, Pearl River, NY, 10965, USA
venkata@wyeth.com
SOURCE: Journal of Medicinal Chemistry, (December 2 2004) Vol. 47, No. 25, pp. 6255-6269. print.
ISSN: 0022-2623 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2005
Last Updated on STN: 9 Mar 2005
ED Entered STN: 9 Mar 2005
Last Updated on STN: 9 Mar 2005
AB A series of 4-alkynyloxy phenyl sulfanyl, sulfinyl and sulfony alkyl and piperidine-4-carboxylic acid **hydroxamides** were synthesized. Their structure-activity relationships, against **tumor necrosis** factor-alpha (**TACE**) and **matrix metalloproteinase** (NIMP) inhibitor activities, are presented by investigating the oxidation state on sulfur and altering the P1' substituent. The sulfonyl derivatives 20-24 carrying a 4-butynyloxy moiety were selective **TACE** inhibitors over the **MMPs** tested. The sulfinyl derivatives showed a preference for a specific oxidation on sulfur as in compounds 25-28. The selectivity over **MMPs** was also demonstrated in the sulfonyl series. The enhanced cellular activity was achieved upon incorporating a butynyloxy substituent in the piperidene series. Compounds 64 and 65 were potent inhibitors of **TNF**-alpha release in the mouse at 100 mg/kg po.
CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Chemicals & Biochemicals
4-alkynyloxy phenly sulfanyl; **matrix metalloproteinase inhibitor**; piperidine-4-carboxylic acid **hydroxamides**; sulfinyl; sulfonyl alkyl **hydroxamate**; sulfur: oxidation state; **tumor necrosis factor-alpha**
IT Miscellaneous Descriptors
structure-activity relationship
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 13827-32-2 (sulfinyl)
7704-34-9 (sulfur)

L51 ANSWER 40 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:175141 BIOSIS
DOCUMENT NUMBER: PREV200400176872
TITLE: Crystal structure of the catalytic domain of human **matrix metalloproteinase** 10.
AUTHOR(S): Bertini, I. [Reprint Author]; Calderone, V.; Fragai, M.; Luchinat, C.; Mangani, S.; Terni, B.
CORPORATE SOURCE: CERM, University of Florence and FiorGen Foundation, Via Sacconi 6, 50019, Sesto Fiorentino, Florence, Italy bertini@cerm.unifi.it
SOURCE: Journal of Molecular Biology, (20 February 2004) Vol. 336, No. 3, pp. 707-716. print.
ISSN: 0022-2836 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
ED Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
AB The catalytic domain of **matrix metalloproteinase**-10 (**MMP**-10) has been expressed in Escherichia coli and its crystal structure solved at 2.1 ANG resolution. The availability of this structure allowed us to critically examine the small differences existing between the catalytic domains of **MMP**-3 and **MMP**-10, which show the highest sequence identity among all **MMPs**. Furthermore, the binding mode of N-isobutyl-N-(4-**methoxyphenylsulfonyl**)glycyl **hydroxamic** acid (NNGH), which is one of the most known commercial inhibitors of **MMPs**, is described for the first time.
CC Enzymes - General and comparative studies: coenzymes 10802
Physiology and biochemistry of bacteria 31000
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
N-isobutyl-N-[4-methoxy-phenylsulfonyl]glycyl hydroxamic acid: matrix metalloproteinase inhibitor; human **matrix metalloproteinase** 10: catalytic domain crystal structure
ORGN Classifier
Enterobacteriaceae 06702
Super Taxa
Facultatively Anaerobic Gram-Negative Rods; Eubacteria; Bacteria; Microorganisms
Organism Name
Escherichia coli (species)
Taxa Notes
Bacteria, Eubacteria, Microorganisms
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L51 ANSWER 41 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:420040 BIOSIS
DOCUMENT NUMBER: PREV200400420575
TITLE: New radioiodinated carboxylic and **hydroxamic matrix metalloproteinase** inhibitor tracers as potential tumor imaging agents.
AUTHOR(S): Oltenfreiter, Ruth [Reprint Author]; Staelens, Ludovicus; Lejeune, Annabelle; Dumont, Filip; Frankenne, Francis; Foidart, Jean-Michel; Slegers, Guido
CORPORATE SOURCE: Dept Radiopharm, State Univ Ghent, Harelbekestr 72, B-9000, Ghent, Belgium
ruth.oltenfreiter@rug.ac.be
SOURCE: Nuclear Medicine and Biology, (May 2004) Vol. 31, No. 4, pp. 459-468. print.
ISSN: 0969-8051.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Nov 2004
Last Updated on STN: 3 Nov 2004
ED Entered STN: 3 Nov 2004
Last Updated on STN: 3 Nov 2004
AB Several studies have demonstrated a positive correlation between tumor progression and expression of extracellular proteinases such as **matrix metalloproteinases (MMPs)**. **MMP**-2 and **MMP**-9 have become attractive targets for cancer research because of their increased expression in human malignant tumor tissues of various organs, providing a target for medical imaging techniques. Radioiodinated carboxylic and **hydroxamic MMP** inhibitors 2-(4'-(123)iodo-**biphenyl**-4-sulfonylainino)-3-(1H-indol-3-yl)-propionic acid (9) and 2-(4'-(123I) iodo-biphenyl-4-sulfonylamino)-3-(1H-indol-3-yl)-propionamide (11) were synthesized by electrophilic aromatic substitution of the tributylstannyl derivatives and resulted in radiochemical yields of 60% +/- 5% (n - 3) and 70% +/- 5% (n = 6), respectively. In vitro zymography and enzyme assays showed high inhibition capacities of the inhibitors on gelatinases. In vivo biodistribution showed no long-terin accumulation in organs and the possibility to accumulate in the tumor. These results warrant further studies of radioiodinated carboxylic and **hydroxamic** MNIP inhibitor tracers as potential SPECT tumor imaging agents.
CC Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
2-(4'-iodo-biphenyl-4-sulfonylamino)-3-(1H-indol--yl)-propionamide: biodistribution, carboxylic matrix metalloproteinase inhibitor tracer, hydroxamic matric metalloproteinase inhibitor tracer, iodine-123-labeled, radioiodinated, synthesis, tumor imaging agents, pharmaceutical; 2-(4'-iodo-biphenyl-4-sulfonylamino)-3-(1H-indol-3-yl)-propionic acid: biodistribution, carboxylic matrix metalloproteinase inhibitor tracer, hydroxamic matric metalloproteinase inhibitor tracer, iodine-123-labeled, radioiodinated, synthesis, tumor

imaging agents, pharmaceutical
IT Methods & Equipment
single photon emission computed tomography [SPECT]: imaging and microscopy techniques, laboratory techniques; zymography: electrophoretic techniques, laboratory techniques

L51 ANSWER 42 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:173933 BIOSIS
DOCUMENT NUMBER: PREV200400175275
TITLE: **Succinylhydroxamic** derivatives of alpha-amino acids as **MMP** inhibitors. Study of complex-formation equilibria with Cu2+, Ni2+ and Zn2+.
AUTHOR(S): Tegoni, Matteo; Dallavalle, Francesco; Santos, M. Amelia [Reprint Author]
CORPORATE SOURCE: Centro de Quimica Estrutural, Instituto Superior Tecnico, Av Rovisco Pais 1, 1049-001, Lisboa, Portugal
masantos@ist.utl.pt
SOURCE: Journal of Inorganic Biochemistry, (February 2004) Vol. 98, No. 2, pp. 209-218. print.
ISSN: 0162-0134 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
ED Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
AB A series of Pro- and Phe-succinyl **hydroxamate** derivatives, whose nanomolar inhibitory activity towards a series of **matrix metalloproteinases** (**MMPs**) was previously reported, have been studied and described herein in their interaction with Cu2+, Zn2+, Ni2+ in aqueous solution, by using potentiometric, spectroscopic and ESI-MS (electrospray ionization mass) spectrometric techniques. A systematic study at various ligand-to-metal molar ratios allowed the determination of the stability constants of the complexes as well as the estimation of the coordination modes. The similarity in the biological activity of these compounds seems to be paralleled by the identical metal-complexation behaviour at neutral pH, namely in terms of chelating effectiveness and coordination modes, irrespective of the presence of one carboxylic or **hydroxamate** as extra groups, or also of the type of amino-acid residue at the other flank of the succinyl chain, which seems to be enough away from the succinyl **hydroxamate** metal-binding group. The stability order of the metal complexes with these ligands follows the Irving-Williams trend for this type of complex systems. Noteworthy is the identification of an interesting pentanuclear copper(II) species with the **monohydroxamic** ligands which structure was ascribed to a 12-metallacrown-4.
CC Biochemistry studies - Minerals 10069
Enzymes - General and comparative studies: coenzymes 10802
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
copper ion; **matrix metalloproteinase: inhibition**; nickel ion; **phenylalanine**-succinyl **hydroxamate** derivative: enzyme inhibitor; proline-succinyl **hydroxamate** derivative: enzyme inhibitor; zinc ion
IT Methods & Equipment
electrospray ionization mass spectrometry: laboratory techniques, spectrum analysis techniques; potentiometry: laboratory techniques; spectrophotometry: laboratory techniques, spectrum analysis techniques;

spectropolarimetry: laboratory techniques, spectrum analysis techniques
RN 15158-11-9 (copper ion)
141907-41-7 (**matrix metalloproteinase**)
14701-22-5 (nickel ion)
23713-49-7 (zinc ion)

L51 ANSWER 43 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:118406 BIOSIS
DOCUMENT NUMBER: PREV200400123646
TITLE: Reduction of experimental laser-induced choroidal neovascularization by orally administered BPHA, a selective **metalloproteinase** inhibitor.
AUTHOR(S): Kohri, Takashi [Reprint Author]; Moriwaki, Mitsuyasu; Nakajima, Masatoshi; Tabuchi, Hitoshi; Shiraki, Kunihiko
CORPORATE SOURCE: Department of Ophthalmology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno-ku, 545-8585, Osaka City, Japan
kohri@med.osaka-cu.ac.jp
SOURCE: Graefe's Archive for Clinical and Experimental Ophthalmology, (November 2003) Vol. 241, No. 11, pp. 943-952. print.
CODEN: GACODL. ISSN: 0721-832X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
ED Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB Background: N-**Biphenyl** sulfonyl-**phenylalanine** **hydroxamic** acid (BPHA), a synthetic, selective **matrix** **metalloproteinase** (**MMP**)-2, -9, -14 inhibitor, has been reported to show significant antiangiogenic activity without unpleasant adverse effects. After film in situ zymography (FIZ) and conventional zymography were performed to detect **MMP** in experimental choroidal neovascularizations (CNVs), we studied the reducible effect of BPHA on CNVs. Methods: Using FIZ, the gelatinolytic activity of **MMP** and BPHA-reduction on gelatinolysis were examined in diode-laser-induced CNV lesions in a total of 22 male Brown Norway rats. The **MMP** subtypes were studied in the CNV lesions of three rats using conventional zymography. Vehicle solution only or 25-, 50-, or 100 mg/kg-body-weight of BPHA was administered orally twice daily for 14 days after the laser photocoagulation in 18 rats, respectively. Fluorescein angiograms were taken, and the late hyperfluorescence of CNVs was given scores by three researchers using four grades. The thickness of CNV lesions was studied histologically. Results: In laser-induced CNVs, the gelatinolytic activity of **MMP** and reduction of gelatinolysis by BPHA were observed on FIZ, and **MMP**-2 and proMMP-2 were identified by conventional zymography. The scores given to the late dye leakage and staining on angiograms were lower in the BPHA-treated groups ($p<0.01$) than in the controls, and the effect appeared to be dose-dependent. Similarly, the CNV lesions in the BPHA-treated groups were less thick than in the controls ($p<0.01$). Conclusions: **MMP** -2 played a role in laser-induced CNV development, and administration of BPHA reduced the experimental CNVs.
CC Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Sense organs - Physiology and biochemistry 20004
Sense organs - Pathology 20006
Pharmacology - General 22002

IT Major Concepts
Methods and Techniques; Pharmacology; Sense Organs (Sensory Reception)
IT Diseases
experimental laser-induced choroidal neovascularization: eye disease, injury, complications
IT Chemicals & Biochemicals
N-**biphenyl** sulfonyl-**phenylalanine** **hydroxamic** acid [BPHA]: enzyme inhibitor-drug; **matrix metalloproteinase-2 [MMP-2]**
IT Methods & Equipment
conventional zymography: laboratory techniques
IT Miscellaneous Descriptors
gelatinolysis
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Brown Norway rat (common): male
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 146480-35-5 (**matrix metalloproteinase**-2)
146480-35-5 (**MMP**-2)

L51 ANSWER 44 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:127804 BIOSIS
DOCUMENT NUMBER: PREV200300127804
TITLE: Synthesis and structure-activity relationships of 5,6,7,8-tetrahydropyrido(3,4-b)pyrazine-based **hydroxamic** acids as HB-EGF shedding inhibitors.
AUTHOR(S): Yoshiizumi, Kazuya [Reprint Author]; Yamamoto, Minoru; Miyasaka, Tomohiro; Ito, Yasuko; Kumihara, Hiroshi; Sawa, Masaaki; Kiyoi, Takao; Yamamoto, Takeshi; Nakajima, Fumio; Hirayama, Ryoichi; Kondo, Hirosato; Ishibushi, Etsuko; Ohmoto, Hiroshi; Inoue, Yoshimasa; Yoshino, Kohichiro
CORPORATE SOURCE: Medicinal Chemistry Department, Organon Laboratories Ltd., Newhouse, Motherwell, Lanarkshire, ML1 5SH, UK
k.yoshiizumi@organon.nhe.akzonobel.nl
SOURCE: Bioorganic & Medicinal Chemistry, (6 February 2003) Vol. 11, No. 3, pp. 433-450. print.
ISSN: 0968-0896 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB HB-EGF Shedding inhibitors have been expected to become effective medicines for skin diseases caused by the proliferation of keratinocytes. In order to discover novel HB-EGF shedding inhibitors and clarify their structure-activity relationships, 5,6,7,8-**tetrahydronaphthylidine** -based **hydroxamic** acid and 5,6,7,8-tetrahydropyrido(3,4-b)pyrazine-based **hydroxamic** acids have been synthesized. Among the synthesized compounds, the ethoxyethoxy derivative and the methoxypropoxy derivative exhibited much more potent HB-EGF shedding inhibitory activity than CGS 27023A. The structural modification of 5,6,7,8-tetrahydropyrido(3,4-b)pyrazine-based **hydroxamic** acids enabled us to establish the following structure-activity relationships;

the existences of the **hydroxamic** acid, the sulfonamide, and the **phenyl** moieties are crucial for a potent HB-EGF shedding inhibitory activity, and the stereochemistry of the alpha carbon of **hydroxamic** acid is also important. In addition, from the comparison of their HB-EGF shedding inhibitory activities with their **MMPs** inhibitory activities, we found that the S1' pocket of the responsible enzyme for HB-EGF shedding is deep unlike that of **MMP**-1.

CC Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Endocrine - General 17002
Integumentary system - Physiology and biochemistry 18504
Integumentary system - Pathology 18506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Integumentary system, dental and oral biology 22020

IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis); Pharmacology

IT Parts, Structures, & Systems of Organisms
epidermis: integumentary system; keratinocytes: integumentary system

IT Diseases
skin diseases: integumentary system disease
Skin Diseases (MeSH)

IT Chemicals & Biochemicals
5,6,7,8-tetrahydropyrido[3,4-b]pyrazine; 5,6,7,8-tetrahydropyrido[3,4-b]pyrazine-based **hydroxamic** acids: dermatological-drug, heparin-binding-epidermal growth factor shedding inhibitors, structure-activity relationships, synthesis; CGS 27023A: dermatological-drug; a disintegrin and **metalloproteinases**; amphiregulin; epidermal growth factor; fibroblast growth factor-1; heparin-binding-epidermal growth factor; hepatocyte growth factor; **hydroxamic acid**; **matrix metalloproteinase-1**; transforming growth factor alpha

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 169799-04-6 (CGS 27023A)
117147-70-3 (amphiregulin)
62229-50-9 (epidermal growth factor)
106096-92-8 (fibroblast growth factor-1)
9001-12-1 (**matrix metalloproteinase**-1)

L51 ANSWER 45 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:60921 BIOSIS
DOCUMENT NUMBER: PREV200300060921
TITLE: NMR-based modification of **matrix metalloproteinase** inhibitors with improved bioavailability.
AUTHOR(S): Hajduk, Philip J.; Shuker, Suzanne B.; Nettesheim, David G.; Craig, Richard; Augeri, David J.; Betebenner, David; Albert, Daniel H.; Guo, Yan; Meadows, Robert P.; Xu,

Lianhong; Michaelides, Michael; Davidsen, Steven K.; Fesik, Stephen W. [Reprint Author]
CORPORATE SOURCE: Abbott Laboratories, 100 Abbott Park Road, D460, AP-10, Abbott Park, IL, 60064-3500, USA
stephen.fesik@abbott.com
SOURCE: Journal of Medicinal Chemistry, (December 19 2002) Vol. 45, No. 26, pp. 5628-5639. print.
ISSN: 0022-2623 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jan 2003
Last Updated on STN: 22 Jan 2003

ED Entered STN: 22 Jan 2003
Last Updated on STN: 22 Jan 2003
AB The NMR-based discovery of biaryl **hydroxamate** inhibitors of the **matrix metalloproteinase** stromelysin (**MMP**-3) has been previously described (Hajduk et al. J. Am. Chemical Society 1997, 119, 5818-5827). While potent in vitro, these inhibitors exhibited no in vivo activity due, at least in part, to the poor pharmacokinetic properties of the **alkylhydroxamate** moiety. To circumvent this liability, NMR-based screening was implemented to identify alternative zinc-chelating groups. Using this technique, 1-**naphthyl hydroxamate** was found to bind tightly to the protein (KD=50 muM) and was identified as a candidate for incorporation into the lead series. On the basis of NMR-derived structural information, the **naphthyl hydroxamate** and biaryl fragments were linked together to yield inhibitors of this enzyme that exhibited improved bioavailability. These studies demonstrate that the NMR-based screening of fragments can be effectively applied to improve the physicochemical or pharmacokinetic profile of lead compounds.
CC Biochemistry studies - General 10060
Biochemistry studies - Minerals 10069
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Chemicals & Biochemicals
1-**naphthyl hydroxamate**; **matrix metalloproteinase inhibitors**: **bioavailability**; **matrix metalloproteinase-3 [stromelysin]**; zinc
IT Methods & Equipment
NMR: laboratory techniques, spectrum analysis techniques
RN 79955-99-0 (**matrix metalloproteinase**-3)
79955-99-0 (stromelysin)
7440-66-6 (zinc)

L51 ANSWER 46 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:392198 BIOSIS
DOCUMENT NUMBER: PREV200200392198
TITLE: Selective **matrix metalloproteinase** inhibitor, N-**biphenyl** sulfonyl **phenylalanine hydroxamic** acid, inhibits the migration of CD4+ T lymphocytes in patients with HTLV-I-associated myelopathy.
AUTHOR(S): Ikegami, Mayumi; Umehara, Fujio [Reprint author]; Ikegami, Naohito; Maekawa, Ryuji; Osame, Mitsuhiro
CORPORATE SOURCE: The Third Department of Internal Medicine, Kagoshima University, School of Medicine, Sakuragaoka 8-35-1, 890, Kagoshima, Japan
umehara@m2.kufm.kagoshima-u.ac.jp
SOURCE: Journal of Neuroimmunology, (June, 2002) Vol. 127, No. 1-2,

pp. 134-138. print.
CODEN: JNRIDW. ISSN: 0165-5728.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Jul 2002
Last Updated on STN: 17 Jul 2002

ED Entered STN: 17 Jul 2002
Last Updated on STN: 17 Jul 2002

AB **Matrix metalloproteinases** (**MMPs**) have been reported to be involved in various inflammatory disorders. Previous studies revealed that **MMP**-2 and **MMP**-9 might play important roles in the breakdown of the blood-brain barrier (BBB) in the central nervous system (CNS) of patients with HTLV-I-associated myelopathy (HAM)/tropical spastic paraparesis (TSP). N-**Biphenyl** sulfonyl-**phenylalanine hydroxamic** acid (BPHA) selectively inhibits **MMP**-2, -9 and -14, but not **MMP**-1, -3 and -7. In the present study, we examined whether or not the selective **MMP** inhibitor BPHA could inhibit the heightened migrating activity of CD4+ T cells in HAM/TSP patients. The migration assay using an invasion chamber showed that migration of CD4+ T cells in HAM/TSP patients was inhibited by 25 muM BPHA. In addition, the inhibitory ratio of migrating CD4+ lymphocytes was higher in HAM patients compared to normal controls. These results suggest that the selective **MMP** inhibitor BPHA has therapeutic potential for HAM/TSP.

CC Cytology - Animal 02506
Cytology - Human 02508
Enzymes - General and comparative studies: coenzymes 10802
Cardiovascular system - Physiology and biochemistry 14504
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Muscle - Pathology 17506
Bones, joints, fasciae, connective and adipose tissue - Pathology 18006
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Infection; Neurology (Human Medicine, Medical Sciences); Orthopedics (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
CD4-positive T lymphocytes: blood and lymphatics, immune system, inhibition, migration; blood-brain barrier: circulatory system, nervous system; central nervous system: nervous system

IT Diseases
human T-cell lymphotropic virus type I-associated myelopathy: muscle disease, nervous system disease, viral disease, tropical spastic paraparesis
Paraparesis, Tropical Spastic (MeSH)

IT Chemicals & Biochemicals
N-**biphenyl** sulfonyl **phenylalanine hydroxamic** acid: selective **matrix metalloproteinase** inhibitor; **matrix metalloproteinase-2** ; **matrix metalloproteinase-9**

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
human T-cell lymphotropic virus type I: pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 146480-35-5 (**matrix metalloproteinase**-2)
146480-36-6 (**matrix metalloproteinase**-9)

L51 ANSWER 47 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:522206 BIOSIS
DOCUMENT NUMBER: PREV200100522206
TITLE: Discovery of macrocyclic **hydroxamic** acids containing **biphenylmethyl** derivatives at P1', a series of selective **TNF-alpha converting** enzyme inhibitors with potent cellular activity in the inhibition of **TNF-alpha** release.
AUTHOR(S): Xue, Chu-Biao [Reprint author]; He, Xiaohua; Corbett, Ronald L.; Roderick, John; Wasserman, Zelda R.; Liu, Rui-Qin; Jaffee, Bruce D.; Covington, Maryanne B.; Qian, Mingxin; Trzaskos, James M.; Newton, Robert C.; Magolda, Ronald L.; Wexler, Ruth R.; Decicco, Carl P.
CORPORATE SOURCE: Experimental Station, DuPont Pharmaceuticals Company, Wilmington, DE, 19880-0500, USA
chu-biao.xue@dupontpharma.com
SOURCE: Journal of Medicinal Chemistry, (October 11, 2001) Vol. 44, No. 21, pp. 3351-3354. print.
CODEN: JMCMAR. ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Nov 2001
Last Updated on STN: 23 Feb 2002
ED Entered STN: 7 Nov 2001
Last Updated on STN: 23 Feb 2002
AB SAR exploration at P1' using an anti-succinate-based macrocyclic **hydroxamic** acid as a template led to the identification of several bulky biphenylmethyl P1' derivatives which confer potent porcine **TACE** and anti-**TNF**-alpha cellular activities with high selectivity versus most of the **MMPs** screened. Our studies demonstrate for the first time that **TACE** has a larger S1' pocket in comparison to **MMPs** and that potent and selective **TACE** inhibitors can be achieved by incorporation of sterically bulky P1' residues.
CC Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Pharmacology - General 22002
IT Major Concepts
Pharmacology
IT Chemicals & Biochemicals
MMP; **TNF-alpha converting** enzyme inhibitors; biphenylmethyl derivatives; macrocyclic **hydroxamic** acids: discovery, potent cellular activity;

tumor necrosis factor-alpha: release
IT Methods & Equipment
chemical synthesis: synthetic method

L51 ANSWER 48 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:261915 BIOSIS
DOCUMENT NUMBER: PREV200000261915
TITLE: Protease inhibitors: Synthesis of potent bacterial collagenase and **matrix metalloproteinase** inhibitors incorporating N-4-**nitrobenzylsulfonylglycine hydroxamate** moieties.
AUTHOR(S): Scozzafava, Andrea; Supuran, Claudiu T. [Reprint author]
CORPORATE SOURCE: Laboratorio di Chimica Inorganica e Bioinorganica, Universita degli Studi, Via Gino Capponi 7, I-50121, Florence, Italy
SOURCE: Journal of Medicinal Chemistry, (May 4, 2000) Vol. 43, No. 9, pp. 1858-1865. print.
CODEN: JMCMAR. ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002
ED Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002
AB A series of compounds was prepared by reaction of alkyl/arylsulfonyl halides with N-4-nitrobenzylglycine, followed by conversion of the COOH to the CONHOH group, with hydroxylamine in the presence of carbodiimides. Other structurally related compounds were obtained by reaction of N-4-nitrobenzylglycine with aryl isocyanates, arylsulfonyl isocyanates, or benzoyl isothiocyanate, followed by the similar conversion of the COOH into the CONHOH moiety. Another subseries of derivatives was prepared from sulfanilyl- or metanilyl-4-nitrobenzylglycine by reaction with arylsulfonyl isocyanates, followed by conversion of the COOH to the **hydroxamate** moiety. The new compounds were assayed as inhibitors of four **matrix metalloproteinases** (**MMPs**), **MMP**-1, **MMP**-2, **MMP**-8, and **MMP**-9, and of the Clostridium histolyticum collagenase (ChC). Some of the prepared **hydroxamate** derivatives proved to be very effective collagenase/gelatinase inhibitors, depending on the substitution pattern at the sulfonamido moiety. Substitutions leading to best inhibitors of **MMP**-1, a short pocket enzyme, were those involving pentafluorophenylsulfonyl or 3-trifluoromethylphenylsulfonyl moieties at P1' (KI's of 3-5 nM). For **MMP**-2, **MMP**-8, and **MMP**-9 (deep-pocket enzymes), best inhibitors were especially those containing long perfluoroalkylsulfonyl and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl, 3- and 4-carboxyphenylsulfonyl, arylsulfonylureido, or arylsulfonylureidosulfanilyl/metanilyl moieties, at P1'. Bulkier groups in this position, such as 1- and 2-naphthyl, substituted-naphthyl, or quinolin-8-yl moieties among others, led to less effective **MMP**/ChC inhibitors. Best ChC inhibitors were again those containing pentafluorophenylsulfonyl or 3- and 4-protected-aminophenylsulfonyl P1' anchoring groups, suggesting that this protease is also a short-pocket wider-neck one (more similar to **MMP**-1). This study also proves that the 4-nitrobenzyl moiety is an efficient P2' anchoring moiety and that sulfonylureido, ureido, or carboxythioureido substitutions at P1' are also tolerated for obtaining potent sulfonylated amino acid **hydroxamate**-like **MMP**/ChC inhibitors.

CC Pharmacology - General 22002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
Physiology and biochemistry of bacteria 31000
Biophysics - Molecular properties and macromolecules 10506
Enzymes - Physiological studies 10808
IT Major Concepts
Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
collagenase [EC 3.4.24.3]; **matrix metalloproteinase-1**; **matrix metalloproteinase-2**; **matrix metalloproteinase-8**; **matrix metalloproteinase-9**; protease inhibitor: synthesis
IT Methods & Equipment
chemical synthesis: synthetic method
IT Miscellaneous Descriptors
drug development
ORGN Classifier
Endospore-forming Gram-Positives 07810
Super Taxa
Eubacteria; Bacteria; Microorganisms
Organism Name
Clostridium histolyticum
Taxa Notes
Bacteria, Eubacteria, Microorganisms
RN 9001-12-1 (collagenase)
9001-12-1 (EC 3.4.24.3)
9001-12-1 (**matrix metalloproteinase**-1)
146480-35-5 (**matrix metalloproteinase**-2)
9001-12-1 (**matrix metalloproteinase**-8)
146480-36-6 (**matrix metalloproteinase**-9)
37205-61-1 (protease inhibitor)

L51 ANSWER 49 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:373549 BIOSIS
DOCUMENT NUMBER: PREV200000373549
TITLE: Protease inhibitors: Part 12. Synthesis of potent **matrix metalloproteinase** and bacterial collagenase inhibitors incorporating sulfonylated N-4-**nitrobenzyl**-beta-alanine **hydroxamate** moieties.
AUTHOR(S): Scozzafava, Andrea; Ilies, Marc A.; Manole, Gheorghe; Supuran, Claudiu T. [Reprint author]
CORPORATE SOURCE: Laboratorio di Chimica Inorganica e Bioinorganica, Universita degli Studi, Via Gino Capponi 7, I-50121, Florence, Italy
SOURCE: European Journal of Pharmaceutical Sciences, (July, 2000) Vol. 11, No. 1, pp. 69-79. print.
ISSN: 0928-0987.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Aug 2000
Last Updated on STN: 8 Jan 2002
ED Entered STN: 30 Aug 2000
Last Updated on STN: 8 Jan 2002
AB N-4-Nitrobenzyl-beta-alanine was reacted with alkyl/arylsulfonyl halides, followed by conversion of the COOH to the CONHOH group. Structurally related compounds were obtained by reaction of N-4-nitrobenzyl-beta-alanine with aryl isocyanates, arylsulfonyl isocyanates or benzoyl isothiocyanate, followed by similar conversion of the COOH into the CONHOH

moiety. Another subseries of derivatives was prepared from sulfanilyl- or metanilyl-4-nitrobenzyl-beta-alanine by reaction with arylsulfonyl isocyanates, followed by the introduction of the **hydroxamate** moiety. The new compounds were assayed as inhibitors of four **matrix metalloproteinases** (**MMPs**), **MMP**-1, **MMP**-2, **MMP**-8 and **MMP**-9, and of the Clostridium histolyticum collagenase (ChC). Some of the prepared **hydroxamate** derivatives proved to be very effective collagenase/gelatinase inhibitors, depending on the substitution pattern at the sulfonamido moiety. Substitutions leading to the best inhibitors of **MMP**-1, a short-pocket enzyme, were those involving pentafluorophenylsulfonyl or 3-trifluoromethyl-phenylsulfonyl at P1' (KI of 3-5 nM). For **MMP**-2, **MMP**-8 and **MMP**-9 (deep-pocket enzymes), the best inhibitors were those containing perfluoroalkylsulfonyl- and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl-, 3- and 4-carboxy-phenylsulfonyl-, arylsulfonylureido- or arylsulfonylureido-sulfanilyl-/metanilyl moieties at P1'. Bulkier groups in this position, such as 1- and 2-naphthyl-, substituted-naphthyl or quinoline-8-yl- moieties, among others, led to less effective **MMP**/ChC inhibitors. The best ChC inhibitors were again those containing pentafluorophenylsulfonyl, 3- and 4-protected-aminophenylsulfonyl P1' groups. This study demonstrates that the 4-nitrobenzyl moiety, investigated here for the first time, is an efficient P2' anchoring moiety, whereas the beta-alanyl scaffold can successfully replace the alpha-amino acyl one, for obtaining potent **MMP**/ChC inhibitors.

CC Physiology and biochemistry of bacteria 31000
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002

IT Major Concepts
Pharmacology

IT Chemicals & Biochemicals
N-4-nitrobenzyl-beta-alanine; bacterial collagenase; bacterial collagenase inhibitors; **hydroxamate**; **matrix metalloproteinase-1 [MMP-1]**; **matrix metalloproteinase-2 [MMP-2]**; **matrix metalloproteinase-8 [MMP-8]**; **matrix metalloproteinase-9 [MMP-9]**; sulfonyl halide

ORGN Classifier
Endospore-forming Gram-Positives 07810
Super Taxa
Eubacteria; Bacteria; Microorganisms
Organism Name
Clostridium histolyticum
Taxa Notes
Bacteria, Eubacteria, Microorganisms

RN 9001-12-1 (**matrix metalloproteinase**-1)
9001-12-1 (**MMP**-1)
146480-35-5 (**matrix metalloproteinase**-2)
146480-35-5 (**MMP**-2)
9001-12-1 (**matrix metalloproteinase**-8)
9001-12-1 (**MMP**-8)
146480-36-6 (**matrix metalloproteinase**-9)
146480-36-6 (**MMP**-9)

L51 ANSWER 50 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:222734 BIOSIS
DOCUMENT NUMBER: PREV200000222734
TITLE: Novel 4-substituted **phenylsulfanyl** alkyl and aryl

hydroxamic acid **TACE** and **MMP** inhibitors.

AUTHOR(S): Davis, Jamie M. [Reprint author]; Venkatesan, Aranapakam [Reprint author]; Baker, Jannie L. [Reprint author]; Grosu, George T. [Reprint author]; Ellingboe, John W. [Reprint author]; Zask, Arie [Reprint author]; Skotnicki, Jerauld [Reprint author]; Killar, Loran; Cowling, Rebecca [Reprint author]; Jin, Guixian [Reprint author]; Sharr, Michelle; Sung, Amy

CORPORATE SOURCE: Chemical Sciences, Wyeth-Ayerst Research, 401 N. Middletown Rd, Pearl River, NY, 10965, USA

SOURCE: Abstracts of Papers American Chemical Society, (2000) Vol. 219, No. 1-2, pp. MEDI 281. print.
Meeting Info.: 219th Meeting of the American Chemical Society. San Francisco, California, USA. March 26-30, 2000. American Chemical Society.
CODEN: ACSRAL. ISSN: 0065-7727.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 31 May 2000
Last Updated on STN: 5 Jan 2002

ED Entered STN: 31 May 2000
Last Updated on STN: 5 Jan 2002

CC Pharmacology - General 22002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Endocrine - General 17002
Immunology - Immunopathology, tissue immunology 34508
Bones, joints, fasciae, connective and adipose tissue - Pathology 18006
Metabolism - Minerals 13010
Pathology - General 12502
Enzymes - General and comparative studies: coenzymes 10802
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Skeletal System (Movement and Support); Pharmacology

IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease, treatment
Arthritis, Rheumatoid (MeSH)

IT Chemicals & Biochemicals
4-substituted **phenylsulfanyl** alkyl **hydroxamic** acids: enzyme inhibitors, molecular properties, pharmaceuticals, pharmacological properties, synthesis; 4-substituted **phenylsulfanyl** aryl **hydroxamic** acids: enzyme inhibitors, molecular properties, pharmaceuticals, pharmacological properties, synthesis; cytokines; enzymes: inhibition

IT Miscellaneous Descriptors
inflammation; pathology; Meeting Abstract

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L51 ANSWER 51 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:396713 BIOSIS
DOCUMENT NUMBER: PREV199800396713
TITLE: Bis-substituted malonic acid **hydroxamate** derivatives as inhibitors of human neutrophil collagenase (MMP8).
AUTHOR(S): Graf Von Roedern, Erich; Brandstetter, Hans; Engh, Richard A.; Bode, Wolfram; Grams, Frank; Moroder, Luis [Reprint author]
CORPORATE SOURCE: Max-Planck-Institut fuer Biochemie, Am Klopferspitz 18A, D-82152 Martinsfied, Germany
SOURCE: Journal of Medicinal Chemistry, (July 30, 1998) Vol. 41, No. 16, pp. 3041-3047. print.
CODEN: JMCMAR. ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Sep 1998
Last Updated on STN: 21 Oct 1998
ED Entered STN: 10 Sep 1998
Last Updated on STN: 21 Oct 1998
AB Malonic acid hydroxamate derivatives bis-substituted at the methylene group were synthesized as potential nonpeptidic inhibitors of human neutrophil collagenase (MMP8). The presence of an aromatic residue both at the C2 malonic acid position and in the C-terminal tail for hydrophobic interactions with the surface-exposed S1 binding site and the S1' pocket of the enzyme, respectively, was found to be sufficient for submicromolar inhibition potencies. For optimal insertion of the aryl amide group into the hydrophobic S1' Docket, spacing of the C-terminal phenyl group by at least a 3C-chain was required. In view of these results the achiral indan-2,2-dicarboxylic acid was used to mimic the 2-benzyl-2-methylmalonic acid residue, and its derivatization to the 3-**phenylpropyl** amide **hydroxamate** produced a potent, achiral, low-mass inhibitor of MMP8 (Ki = 0.3 muM), the binding mode of which was unambiguously determined by X-ray crystallographic analysis.
CC Pharmacology - General 22002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
Biophysics - General 10502
Enzymes - General and comparative studies: coenzymes 10802
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Chemicals & Biochemicals
malonic acid **hydroxamate**: bis-substituted, derivatives, synthesis, potency, enzyme inhibitor; **matrix metalloproteinase 8 [neutrophil collagenase]: inhibition**
IT Methods & Equipment
X-ray crystallography: determination method
IT Miscellaneous Descriptors
pharmaceuticals
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 9001-12-1 (**matrix metalloproteinase** 8)
9001-12-1 (neutrophil collagenase)

L51 ANSWER 52 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:233045 BIOSIS
DOCUMENT NUMBER: PREV199800233045
TITLE: Inhibition of membrane-type 1 **matrix metalloproteinase** by **hydroxamate** inhibitors: An examination of the subsite pocket.
AUTHOR(S): Yamamoto, Minoru; Tsujishita, Hideki; Hori, Noriyuki [Reprint author]; Ohishi, Yuichi; Inoue, Shintaro; Ikeda, Shoji [Reprint author]; Okada, Yasunori
CORPORATE SOURCE: New Drug Discovery Res. Lab., Kanebo Ltd., 1-5-90 Tomobuchi-Cho, Miyakojima-Ku, Osaka 534, Japan
SOURCE: Journal of Medicinal Chemistry, (April 9, 1998) Vol. 41, No. 8, pp. 1209-1217. print.
CODEN: JMCMAR. ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998
ED Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998
AB The membrane-type 1 **matrix metalloproteinase** (MT1-**MMP**) has been reported to mediate the activation of pro-gelatinase A (proMMP-2), which is associated with tumor proliferation and metastasis. MT1-**MMP** can also digest extracellular matrix (ECM) such as interstitial collagens, gelatin, and proteoglycan and thus may play an important role in pathophysiological digestion of ECM. We studied the inhibitory effect of various **hydroxamate MMP** inhibitors, including known inhibitors such as BB-94, BB-2516, GM6001, and Ro31-9790, on a deletion mutant of MT1-**MMP** lacking the transmembrane domain (DELTAMT1) to further characterize the enzyme and develop a selective inhibitor for MT1-**MMP**. The evaluation of the inhibitory activities of various **hydroxamates** reveals general structural profiles affecting selectivities toward **MMPs**. In particular, a longer side chain at the P1' position is preferable for the binding to **MMP**-2, -3, and -9 and MT1-**MMP**. For the P2' position, an alpha-branched alkyl group is critical for the binding toward DELTAMT1, while the introduction of a bulky group at the alpha-position of **hydroxamic** acid seems to diminish the activity against DELTAMT1. Summation of the data on the sensitivity of DELTAMT1 to various **hydroxamate** inhibitors indicates that (1) the volume of the S1' subsite of DELTAMT1 is similar to that of **MMP**-2, -3, and -9, which is bigger than that of **MMP**-1, and (2) the S1 and S2' subsites are narrower than those in other **MMPs**. On the basis of these results, the **hydroxamates** with a P1' **phenylpropyl** and P2' alpha-branched alkyl group were synthesized and evaluated for inhibitory activity. These inhibitors (1h,i) showed strong activity against DELTAMT1 over **MMP**-1, but no selectivity between DELTAMT1 and **MMP**-9. These results are explained using molecular modeling studies conducted on MT1-**MMP**.
CC Pharmacology - General 22002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
Biophysics - General 10502
Enzymes - General and comparative studies: coenzymes 10802
IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Chemicals & Biochemicals
membrane-type 1 **matrix metalloproteinase** [MT1-**MMP**]: deletion mutation, subsite pocket, transmembrane domain, inhibition; BB-2516: enzyme inhibitor-drug, hydroxymate **MMP** inhibitor, quantitative structure-activity relationships; BB-94: enzyme inhibitor-drug, hydroxymate **MMP** inhibitor, quantitative structure-activity relationships; GM6001: enzyme inhibitor-drug, hydroxymate **MMP** inhibitor, quantitative structure-activity relationships; Ro31-9790: enzyme inhibitor-drug, hydroxymate **MMP** inhibitor, quantitative structure-activity relationships
IT Miscellaneous Descriptors
pharmaceutical industry; drug design
RN 161384-17-4 (membrane-type 1 **matrix metalloproteinase**)
161384-17-4 (MT1-**MMP**)
154039-60-8 (BB-2516)
130370-60-4 (BB-94)
145337-55-9 (Ro31-9790)
81669-70-7 (**METALLOPROTEINASE**)

L51 ANSWER 53 OF 85 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:83343 BIOSIS
DOCUMENT NUMBER: PREV200200083343
TITLE: **Biphenyl hydroxamate** inhibitors of **matrix metalloproteinases.**
AUTHOR(S): Fesik, S. W. [Inventor]; Summers, J. B., Jr. [Inventor]; Davidsen, S. K. [Inventor]; Sheppard, G. S. [Inventor]; Steinman, D. H. [Inventor]; Carrera, G. M., Jr. [Inventor]; Florjancic, A. [Inventor]; Holms, J. H. [Inventor]
CORPORATE SOURCE: Gurnee, Ill., USA
ASSIGNEE: ABBOTT LABORATORIES
PATENT INFORMATION: US 5665777 19970909
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sept. 9, 1997) Vol. 1202, No. 2, pp. 1389-1390. print.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2002
Last Updated on STN: 25 Feb 2002
ED Entered STN: 16 Jan 2002
Last Updated on STN: 25 Feb 2002
NCL 514575000
CC Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
Pharmacology - General 22002
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Miscellaneous Descriptors
ENZYME INHIBITOR AGENTS; MOLECULAR STRUCTURE; PHARMACEUTICALS

L51 ANSWER 54 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2005-0390734 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Discovery of 3,3-dimethyl-5-hydroxypipecolic **hydroxamate**-based inhibitors of aggrecanase

and **MMP**-13
AUTHOR: NOE Mark C.; NATARAJAN Vijayalakshmi; SNOW Sheri L.; MITCHELL Peter G.; LOPRESTI-MORROW Lori; REEVES Lisa M.; YOCUM Sue A.; CARTY Thomas J.; BARBERIA John A.; SWEENEY Francis J.; LIRAS Jennifer L.; VAUGHN Marcie; HARDINK Joel R.; HAWKINS Joel M.; TOKAR Christopher
CORPORATE SOURCE: Pfizer Global Research and Development Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2005), 15(11), 2808-2811
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/2 p. ref. et notes
AVAILABILITY: INIST-22446, 354000124636920230
UP 20051010
AB A series of pipecolic **hydroxamate** inhibitors of **MMP**-13 and aggrecanase was discovered based on screening known inhibitors of **TNF**-a converting enzyme (**TACE**). Potency versus aggrecanase was optimized by modification of the benzyloxyaryl-sulfonamide group. Incorporation of geminal alkyl substitution at the 3-position of the piperidine ring improved metabolic stability, presumably by increasing steric hindrance around the metabolically labile **hydroxamic** acid. This modification also resulted in dramatic improvement of aggrecanase activity with a slight reduction in selectivity versus **MMP**-1. Synthesis, structure activity relationships, and strategies to reduce metabolic clearance are described.

L51 ANSWER 55 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2005-0251575 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Synthesis and SAR of diazepine and thiazepine **TACE** and **MMP** inhibitors
AUTHOR: ZASK Arie; KAPLAN Joshua; XUEMEI DU; MACEWAN Gloria; SANDANAYAKA Vincent; EUDY Nancy; LEVIN Jeremy; GUIXIAN JIN; JUN XU; CUMMONS Terri; BARONE Dauphine; AYRAL-KALOUSTIAN Semiramis; SKOTNICKI Jerauld
CORPORATE SOURCE: Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth Research, PO Box CN 8000, Princeton, NJ 08543, United States; Amgen, Seattle, WA 98101, United States
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2005), 15(6), 1641-1645
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/2 p. ref. et notes
AVAILABILITY: INIST-22446, 354000126328090210
UP 20050627
AB Potent and selective TACE and MMP inhibitors utilizing the diazepine and thiazepine ring systems were synthesized and evaluated for biological activity in in vitro and in vivo models of TNF-α release. Oral

activity in the mouse LPS model of TNF-a release was seen. Efficacy in the mouse collagen induced arthritis model was achieved with diazepine 20.

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ACCESSION NUMBER: 2004-0606858 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Pyran-containing sulfonamide **hydroxamic** acids: Potent **MMp** inhibitors that spare **MMP**-1
AUTHOR: REITER Lawrence A.; ROBINSON Ralph P.; MCCLURE Kim F.; JONES Christopher S.; REESE Matthew R.; MITCHELL Peter G.; OTTERNESS Ivan G.; BLIVEN Marcia L.; LIRAS Jennifer; CORTINA Santo R.; DONAHUE Kathleen M.; ESKRA James D.; GRIFFITHS Richard J.; LAME Mary E.; LOPEZ-ANAYA Arturo; MARTINELLI Gary J.; MCGAHEE Shunda M.; YOCUM Sue A.; LOPRESTI-MORROW Lori L.; TOBIASSEN Lisa M.; VAUGHN-BOWSER Marcie L.
CORPORATE SOURCE: Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States; Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2004), 14(13), 3389-3395
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 3/4 ref. et notes
AVAILABILITY: INIST-22446, 354000110389820030
UP 20041223
AB The SAR of a series of sterically hindered sulfonamide **hydroxamic** acids with relatively large P.sub.1' groups is described. The compounds typically spare **MMP**-1 while being potent inhibitors of **MMP**-13. The metabolically more stable compounds in the series contain either a monocyclic or bicyclic pyran ring adjacent to the **hydroxamate** group. Despite the sparing of **MMP**-1, preclinical and clinical studies revealed that fibrosis in rats and MSS in humans is still produced.

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ACCESSION NUMBER: 2004-0593701 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Sultam **hydroxamates** as novel **matrix metalloproteinase** inhibitors
AUTHOR: CHERNEY Robert J.; MO Ruowei; MEYER Dayton T.; HARDMAN Karl D.; LIU Rui-Qin; COVINGTON Maryanne B.; MINGXIN QIAN; WASSERMAN Zelda R.; CHRIST David D.; TRZASKOS James M.; NEWTON Robert C.; DECICCO Carl P.
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, United States
SOURCE: Journal of medicinal chemistry : (Print), (2004), 47(12), 2981-2983, 17 refs.

ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal; (letter to editor)
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000111973820060
UP 20041213
AB In this communication we describe the design, synthesis, and evaluation of novel sultam **hydroxamates** 4 as **MMP**-2, -9, and -13 inhibitors. Compound 26 was found to be an active inhibitor (**MMP** -2 IC.sub.5.sub.0 = 1 nM) with 1000-fold selectivity over **MMP**-1 and good oral bioavailability (F = 43%) in mouse. An X-ray crystal structure of 26 in **MMP**-13 confirms the key hydrogen bonds and prime side binding in the active site.

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ACCESSION NUMBER: 2004-0551388 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Synthesis and biological activity of selective azasugar-based **TACE** inhibitors
AUTHOR: TSUKIDA Takahiro; MORIYAMA Hideki; INOUE Yoshimasa; KONDO Hirosato; YOSHINO Kohichiro; NISHIMURA Shin-Ichiro
CORPORATE SOURCE: Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan; R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan; Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-11, Kita-Ku, Sapporo 001-0021, Japan
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2004), 14(6), 1569-1572
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/2 p. ref. et notes
AVAILABILITY: INIST-22446, 354000116705780410
UP 20041117
AB A series of azasugar-based **hydroxamic** acid derivatives bearing 2R,3R,4R,5R-configuration is described. Compound 4c with 4,5-O-acetonide group showed excellent in vitro potency against **TACE**, with high selectivity over **MMP**-1 and moderate selectivity over **MMP**-3 and **MMP**-9.

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ACCESSION NUMBER: 2004-0280279 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Cyclic phosphinamides and phosphonamides, novel series of potent **matrix metalloproteinase** inhibitors with antitumour activity
AUTHOR: DAHL SORENSEN Morten; BLAEHR Lars K. A.; CHRISTENSEN Mette K.; HOYER Thomas; LATINI Scilla; HJARNAA Pernille-Julia V.; BJOERKLING Fredrik
CORPORATE SOURCE: Medicinal Chemistry Research, LEO Pharma,

Industriparken 55, 2750 Ballerup, Denmark; Department of Biochemistry, LEO Pharma, Industriparken 55, 2750 Ballerup, Denmark; Department of Pharmacology, LED Pharma, Industriparken 55, 2750 Ballerup, Denmark
SOURCE: Bioorganic & medicinal chemistry, (2003), 11(24), 5461-5484, 27 refs.
ISSN: 0968-0896
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-26564, 354000114951660180
UP 20040629
AB The design, synthesis, and structure-activity relationship (SAR) of a series of novel nonpeptidic cyclic phosphon- and phosphinamide-based **hydroxamic** acids as inhibitors of **matrix metalloproteinases MMP**-1, **MMP**-3, and **MMP**-9 are presented. Based on modelling studies and X-ray analysis, a model of the binding mode of these novel compounds in the **MMP** active site was obtained. This model provided a rational explanation for the observed SAR data, which included a systematic study of different S1' directed substituents, zinc-complexing groups, chirality, and variation of the cyclic phosphon- and phosphinamide rings. The in vivo effect of four compounds in a human fibrosarcoma mouse model (HT1080) was evaluated and compared to that of a reference compound. Prinomastat. Inhibition of tumour growth was observed for all four compounds.

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ACCESSION NUMBER: 2004-0335214 PASCAL
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TITLE (IN ENGLISH): Rational design, synthesis and structure-activity relationships of a cyclic succinate series of **TNF**-α **converting** . enzyme inhibitors. Part 1: Lead identification
AUTHOR: XUE Chu-Biao; XIAOHUA HE; RODERICK John; CORBETT Ronald L.; DUAN James J.-W.; LIU Rui-Qin; COVINGTON Maryanne B.; NEWTON Robert C.; TRZASKOS James M.; MAGOLDA Ronald L.; WEXLER Ruth R.; DECICCO Carl P.
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, United States
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2003), 13(24), 4293-4297, 14 refs.
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-22446, 354000114947060070
UP 20040719
AB Rational design based on the broad spectrum MMP inhibitor CGS 27023A led to the identification of a novel series of cyclic succinate TACE inhibitors. As a mixture of two enantiomers, the lead compound 17b exhibited potent enzyme activity (IC.sub.5.sub.0 = 8 nM) in the inhibition of porcine TNF-α converting enzyme (pTACE) and excellent selectivity over aggrecanase and MMP-1, -2 and -9.

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on STN
ACCESSION NUMBER: 2003-0434329 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Design, synthesis and evaluation of novel azasugar-based **MMP**/ADAM inhibitors
AUTHOR: MORIYAMA Hideki; TSUKIDA Takahiro; INOUE Yoshimasa; KONDO Hirosato; YOSHINO Kohichiro; NISHIMURA Shin-Ichiro
CORPORATE SOURCE: Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan; R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan; Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan
SOURCE: Bioorganic & medicinal chemistry letters : (Print), (2003), 13(16), 2741-2744
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/4 p. ref. et notes
AVAILABILITY: INIST-22446, 354000112228260260
UP 20031104
AB In order to verify whether azasugar would be a useful scaffold for inhibitory activity against metalloproteinases, we synthesized some azasugar-based compounds. As a result, it is clarified that azasugar moiety could function as successful inhibitor of matrix metalloproteinase-1, -3 and -9 and TACE.

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on STN
ACCESSION NUMBER: 2003-0354461 PASCAL
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TITLE (IN ENGLISH): Synthesis and structure-activity relationship of N-substituted 4-arylsulfonylpiperidine-4-**hydroxamic** acids as novel, orally active **matrix metalloproteinase** inhibitors for the treatment of osteoarthritis
AUTHOR: ARANAPAKAM Venkatesan; DAVIS Jamie M.; GROSU George T.; BAKER Jannie; ELLINGBOE John; ZASK Arie; LEVIN Jeremy I.; SANDANAYAKA Vincent P.; DU Mila; SKOTNICKI Jerauld S.; DIJOSEPH John F.; SUNG Amy; SHARR Michele A.; KILLAR Loran M.; WALTER Thomas; GUIXIAN JIN; COWLING Rebecca; TILLETT Jeff; WEIGUANG ZHAO; MCDEVITT Joseph; ZHANG BAO XU
CORPORATE SOURCE: Wyeth Research, 401 N. Middletown Road, Pearl River, New York 10965, United States; Wyeth Research, P.O. Box CN-8000, Princeton, New Jersey 08543, United States
SOURCE: Journal of medicinal chemistry : (Print), (2003), 46(12), 2376-2396, 17 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English

AVAILABILITY: INIST-9165, 354000118233340140
UP 20030912
AB The matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that play a key role in both physiological and pathological tissue degradation. In our preceding paper, we have reported on a series of novel and orally active N-hydroxy-α-phenylsulfonyl-acetamide derivatives. However, these compounds had two drawbacks (moderate selectivity and chirality issues). To circumvent these two problems, a series of novel and orally active N-substituted 4-benzenesulfonylpiperidine-4-carboxylic acid hydroxyamide derivatives have been synthesized. The present paper deals with the synthesis and SAR of these compounds. Among the several compounds synthesized, derivative 55 turned out to be a potent, selective, and an orally active MMP inhibitor in the clinically relevant advanced rabbit osteoarthritis model. Detailed pharmacokinetics and metabolism data are described.

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ACCESSION NUMBER: 2003-0260365 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Synthesis and SAR of bicyclic heteroaryl **hydroxamic** acid **MMP** and **TACE** inhibitors
AUTHOR: ZASK A.; GU Y.; ALBRIGHT J. D.; DU X.; HOGAN M.; LEVIN J. I.; CHEN J. M.; KILLAR L. M.; SUNG A.; DIJOSEPH J. F.; SHARR M. A.; ROTH C. E.; SKALA S.; JIN G.; COWLING R.; MOHLER K. M.; BARONE D.; BLACK R.; MARCH C.; SKOTNICKI J. S.
CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth Research, PO Box CN800, Princeton, NJ 08543, United States; Immunex Corporation, Seattle, WA 98101, United States
SOURCE: Bioorganic & medicinal chemistry letters, (2003), 13(8), 1487-1490, 16 refs.
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-22446, 354000110838630200
UP 20030626
AB Potent and selective bicyclic heteroaryl **hydroxamic** acid **MMP** and **TACE** inhibitors were synthesized by a novel convergent route. Selectivity and efficacy versus **MMPs** and **TACE** could be controlled by appropriate substitution on the scaffolds and by variation of the P1' group. Select compounds were found to be effective in in vivo models of arthritis.

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ACCESSION NUMBER: 2004-0119346 PASCAL
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TITLE (IN ENGLISH): Screening of stress enhancer based on analysis of gene expression profiles: Enhancement of hyperthermia-induced **tumor necrosis** by an **MMP**-3 inhibitor
AUTHOR: KATO Naoki; KOBAYASHI Takeshi; HONDA Hiroyuki
CORPORATE SOURCE: Department of Biotechnology, School of Engineering,

Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan
SOURCE: Cancer science, (2003), 94(7), 644-649, 46 refs.
ISSN: 1347-9032
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Japan
LANGUAGE: English
AVAILABILITY: INIST-2432, 354000114967190140
UP 20040323
AB To improve the therapeutic benefit of hyperthermia, we examined changes of global gene expression after heat shock using DNA microarrays consisting of 12 814 clones. HeLa cells were treated for 1 h at 44°C and RNA was extracted from the cells 0, 3, 6, and 12 h after heat shock. The 664 genes that were up or down-regulated after heat shock were classified into 7 clusters using fuzzy adaptive resonance theory (fuzzy ART). There were 41 genes in two clusters that were induced in the early phase after heat shock. In addition to shock response genes, such as hsp70 and hsp40, the stress response genes c-jun, c-fos and egr-1 were expressed in the early phase after heat shock. We also found that expression of **matrix metalloproteinase** 3 (**MMP**-3) was enhanced during the early response. We therefore investigated the role of **MMP**-3 in the heat shock response by examining HeLa cell survival after heat treatment in the presence and absence of an **MMP**-3 inhibitor, N-isobutyl-N-(4-**methoxyphenyl**-sulfonyl)**glycylhydroxamic** acid (NNGH) or N-hydroxy-2(R)-[[4-methoxysulfonyl](3-picolyl)amino]-3-methylbutaneamide hydrochloride (MMI270). The number of surviving cells 3 days after heat treatment significantly decreased, reaching 3.5% for NNGH and 0.2% for MMI270. These results indicate that the **MMP**-3 inhibitors enhanced heat shock-induced cell death and behaved as stress enhancers in cancer cells. This valuable conclusion was reached as a direct result of the gene expression profiling that was performed in these studies.

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ACCESSION NUMBER: 2002-0394701 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Synthesis and biological activity of selective pipecolic acid-based **TNF**-α **converting** enzyme (**TACE**) inhibitors
AUTHOR: LETAVIC Michael A.; AXT Matt Z.; BARBERIA John T.; CARTY Thomas J.; DANLEY Dennis E.; GEOGHEGAN Kieran F.; HALIM Nadia S.; HOTH Lise R.; KAMATH Ajith V.; LAIRD Ellen R.; LOPRESTI-MORROW Lori L.; MCCLURE Kim F.; MITCHELL Peter G.; NATARAJAN Vijayalakshmi; NOE Mark C.; PANDIT Jayvardhan; REEVES Lisa; SCHULTE Gayle K.; SNOW Sheri L.; SWEENEY Francis J.; TAN Douglas H.; YU Chul H.
CORPORATE SOURCE: Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States; Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, United States
SOURCE: Bioorganic & medicinal chemistry letters, (2002), 12(10), 1387-1390
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 3/4 p. ref. et notes
AVAILABILITY: INIST-22446, 354000101241630150
UP 20020821
AB A series of novel, selective **TNF**-α **converting** enzyme inhibitors based on 4-hydroxy and 5-hydroxy pipecolate **hydroxamic** acid scaffolds is described. The potency and selectivity of **TACE** inhibition is dramatically influenced by the nature of the sulfonamide group which interacts with the S1' site of the enzyme. Substituted 4-benzyloxybenzenesulfonamides exhibit excellent **TACE** potency with > 100 x selectivity over inhibition of **matrix metalloprotease**-1 (**MMP**-1). Alkyl substituents on the ortho position of the benzyl ether moiety give the most potent inhibition of **TNF**-α release in LPS-treated human whole blood.

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ACCESSION NUMBER: 2002-0038400 PASCAL
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TITLE (IN ENGLISH): α-Amino-β-sulphone **hydroxamates** as potent **MMP**-13 inhibitors that spare **MMP**-1
AUTHOR: BECKER Daniel P.; BARTA Thomas E.; BEDELL Louis; DECRESCENZO Gary; FRESKOS John; GETMAN Daniel P.; HOCKERMAN Susan L.; LI Madeleine; MEHTA Pramod; MISCHKE Brent; MUNIE Grace E.; SWEARINGEN Craig; VILLAMIL Clara I.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Inflammation-Oncology, Pharmacia Research & Development, 4901 Searle Parkway, Skokie, IL 60077, United States; Departments of Medicinal Chemistry and Inflammation-Oncology, Pharmacia Research & Development, 700 Chesterfield Village Parkway, St. Louis, MO 63198, United States
SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(20), 2719-2722
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/2 p. ref. et notes
AVAILABILITY: INIST-22446, 354000096443790130
UP 20020122
AB A series of α-amino-β-sulphone **hydroxamates** was prepared and evaluated for potency versus **MMP**-13 and selectivity versus **MMP**-1. Various substituents were employed on the α-amino group (P.sub.1 position), as well as different groups attached to the sulphone group extending into P.sub.1'. Low nanomolar potency was obtained for **MMP**-13 with selectivity versus **MMP**-1 of > 1000 x for a number of analogues.

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TITLE (IN ENGLISH): QSAR of **matrix metalloproteinase** inhibitor N-[(substituted **phenyl**)sulfonyl]-N-4-nitrobenzyl-glycine **hydroxamates** using LFER model

AUTHOR: ROY Kunal; DIPAK KUMAR PAL; DE A. U.; SENGUPTA Chandana

CORPORATE SOURCE: Division of Pharmaceutical Chemistry, Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Mayurbhanj 757 086, Orissa, India; QSAR Lab, Division of Medicinal and Pharmaceutical Chemistry, Department of Pharmaceutical Technology, Jadavpur University, Calcutta 700 032, India

SOURCE: Drug design and discovery, (2001), 17(4), 315-323, 13 refs.
ISSN: 1055-9612

DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
AVAILABILITY: INIST-21182, 354000103159360020
UP 20020225

AB QSAR analyses of **matrix metalloproteinase** (**MMP**) inhibitor N-[(substituted **phenyl**)sulfonyl]-N-4-nitrobenzylglycine **hydroxamates**, recently reported by Scozzafava and Supuran, have been attempted using linear free energy related (LFER) model of Hansch to explore the contribution patterns of the phenyl ring substitutions (P.sub.1' anchoring site of the ligands) to the activities against **MMP**-1, -2, -8 and -9 (pC.sub.1, pC.sub.2, pC.sub.8 and pC.sub.9) and C. histolyticum collagenase (pC.sub.C.sub.h.sub.C) and also to find out relations among the activities. Multiple regression analyses applied on the data set reveal that electron withdrawing meta substituents and lipophilic ortho and meta substituents are conducive to pC.sub.1 while presence of substituents (larger than hydrogen) at vicinal positions on the phenyl ring and bulkier ortho substituents are detrimental to the activity. Again, the electronic and steric parameters of meta substituents (σ.sub.m and MR.sub.m) and lipophilicity parameter of ortho substituents (π.sub.o) contribute significantly to pC.sub.2, pC.sub.8 and pC.sub.9:σ.sub.m shows parabolic relationships (optimum σ.sub.m values being 0.518, 0.584 and 0.522 respectively) and steric bulk of meta substituents has negative impact while presence of hydrophilic groups at the ortho positions increases the activities. Further, presence of electron withdrawing meta substituents and hydrophilic para substituents is conducive to the C. histolyticum collagenase (pC.sub.C.sub.h.sub.C) activity. The study suggests that the structural and physicochemical requirements of the P.sub.1' anchoring site for the activities against **MMP**-2, -8 and -9 are highly intercorrelated and these are comparatively less correlated with those for the activities against **MMP**-1 and C. histolyticum collagenase.

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ACCESSION NUMBER: 2001-0123337 PASCAL

TITLE (IN ENGLISH): Heteroaryl and cycloalkyl sulfonamide **hydroxamic** acid inhibitors of **matrix metalloproteinases**

AUTHOR: LEVIN Jeremy I.; YANSONG GU; NELSON Frances C.; ZASK

Arie; DIJOSEPH John F.; SHARR Michele A.; SUNG Amy; GUIXIAN JIN; COWLING Rebecca; CHANDA Pranab; COSMI Scott; HSIAO Chu-Lai; EDRIS Wade; WILHELM James; KILLAR Loran M.; SKOTNICKI Jerauld S.
CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, United States; Wyeth-Ayerst Research, Cambridge, MA 02140, United States
SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(2), 239-242
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/4 p. ref. et notes
AVAILABILITY: INIST-22446, 354000094861770360
UP 20010402
AB Heteroaryl and cycloalkyl sulfonamide-**hydroxamic** acid **MMP** inhibitors were investigated. Of these, the pyridyl analogue 2 is the most potent and selective inhibitor of **MMP**-9 and **MMP**-13 in vitro.

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ACCESSION NUMBER: 2001-0122506 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): The discovery of anthranilic acid-based **MMP** inhibitors. Part 1: SAR of the 3-position
AUTHOR: LEVIN Jeremy I.; DU Mila T.; DIJOSEPH John F.; KILLAR Loran M.; SUNG Amy; WALTER Thomas; SHARR Michele A.; ROTH Catherine E.; MOY Franklin J.; POWERS Robert; GUIXIAN JIN; COWLING Rebecca; SKOTNICKI Jerauld S.
CORPORATE SOURCE: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, United States; Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, United States
SOURCE: Bioorganic & medicinal chemistry letters, (2001), 11(2), 235-238
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
NOTE: 1/2 p. ref. et notes
AVAILABILITY: INIST-22446, 354000094861770350
UP 20010402
AB A novel series of anthranilic acid-based inhibitors of MMP-1, MMP-9, and MMP-13 was prepared and evaluated both in vitro and in vivo. The most potent compound, 6e, has in vivo activity in a rat sponge-wrapped cartilage model.

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ACCESSION NUMBER: 2001-0328742 PASCAL
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TITLE (IN ENGLISH): Development of new **hydroxamate matrix metalloproteinase** inhibitors

derived from functionalized 4-aminoprolines

AUTHOR: NATCHUS Michael G.; BOOKLAND Roger G.; DE Biswanath; ALMSTEAD Neil G.; PIKUL Stanislaw; JANUSZ Michael J.; HEITMEYER Sandra A.; HOOKFIN Erin B.; HSIEH Lily C.; DOWTY Martin E.; DIETSCH Charles R.; PATEL Vikram S.; GARVER Susan M.; FEI GU; POKROSS Matthew E.; MIELING Glen E.; BAKER Timothy R.; FOLTZ David J.; PENG Sean X.; BORNES David M.; STROJNOWSKI Michael J.; TAIWO Yetunde O.

SOURCE: Journal of medicinal chemistry : (Print), (2000), 43(26), 4948-4963, 32 refs.
ISSN: 0022-2623 CODEN: JMCMAR

DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000093588140050
UP 20010821

AB A series of **hydroxamates** was prepared from an aminoproline scaffold and tested for efficacy as **matrix metalloproteinase** (**MMP**) inhibitors. Detailed SAR for the series is reported for five enzymes within the **MMP** family, and a number of inhibitors, such as compound 47, display broad-spectrum activity with sub-nanomolar potency for some enzymes. Modifications of the P1' portion of the molecule played a key role in affecting both potency and selectivity within the **MMP** family. Longer-chain aliphatic substituents in this region of the molecule tended to increase potency for **MMP**-3 and decrease potency for **MMP**-1, as exemplified by compounds 48-50, while aromatic substituents, as in compound 52, generated broad-spectrum inhibition. The data is rationalized based upon X-ray crystal data which is also presented. While the in vitro peroral absorption seemed to be less predictable, it tended to decrease with longer and more hydrophilic substituents. Finally, a rat model of osteoarthritis was used to evaluate the efficacy of these compounds, and a direct link was established between their pharmacokinetics and their in vivo efficacy.

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ACCESSION NUMBER: 2000-0486235 PASCAL
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TITLE (IN ENGLISH): Inhibition of gelatinolytic activity in tumor tissues by synthetic **matrix metalloproteinase** inhibitor : Application of film in situ zymography

AUTHOR: IKEDA M.; MAEKAWA R.; TANAKA H.; MATSUMOTO M.; TAKEDA Y.; TAMURA Y.; NEMORI R.; YOSHIOKA T.

CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka 553-0002, Japan; Ashigara Research Laboratories, Fuji Photo Film Co., Ltd., Kanagawa 250-0193, Japan

SOURCE: Clinical cancer research, (2000), 6(8), 3290-3296, 25 refs.
ISSN: 1078-0432

DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-26073, 354000091246460440
UP 20001127

AB Inhibition of gelatinolytic activity in implanted tumor tissues by oral administration of N-biphenyl sulfonyl-**phenylalanine hydroxamic** acid (BPHA), a selective **matrix metalloproteinase** (**MMP**) inhibitor, was demonstrated by means of film in situ zymography (FIZ). Active-**MMP**-2 but not pro-**MMP**-2 showed gelatinolytic activity in FIZ, whereas both forms of **MMP**-2 were found to be active in conventional zymography. A mixture of either tissue inhibitors of metalloproteinase-2 or BPHA with active-**MMP**-2 resulted in inhibition of gelatinolytic activity in FIZ but not in zymography. Thus, FIZ, but not zymography, could detect net **MMP** activity in tumor tissues. When a specimen from Ma44 human lung cancer xenograft was subjected to FIZ, gelatinolytic activity was markedly detected with precise localization in the tumor tissues. The gelatinolytic activity detected in Ma44 tumor tissues was found to be mainly derived from **MMPs** because the gelatin-degrading activity was inhibited by pretreatment of the tumor specimen with **MMP** inhibitors. Oral administration of BPHA but not (-)BPHA, an enantiomer of BPHA lacking **MMP** inhibitory activity, successfully inhibited the **MMP** activity localized in Ma44 tumor tissues in both a dose-dependent and time-dependent manner. The data presented in this report showed for the first time that oral administration of synthetic **MMP** inhibitor could inhibit the net activity of **MMP** activity in tumor tissues, suggesting the usefulness of the FIZ technique for determining the effective dose of **MMP** inhibitor in clinical studies.

L51 ANSWER 72 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000-0141069 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Design and synthesis of piperazine-based **matrix metalloproteinase** inhibitors
AUTHOR: MENYAN CHENG; BISWANATH DE; PIKUL S.; ALMSTEAD N. G.; NATCHUS M. G.; ANASTASIO M. V.; MCPHAIL S. J.; SNIDER C. E.; TAIWO Y. O.; LONGYIN CHEN; DUNAWAY C. M.; FEI GU; DOWTY M. E.; MIELING G. E.; JANUSZ M. J.; WANG-WEIGAND S.
CORPORATE SOURCE: Procter and Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Road, Mason, Ohio 45040, United States; Procter and Gamble, Corporate Research Division, Miami Valley Laboratories, Cincinnati, Ohio 45253, United States
SOURCE: Journal of medicinal chemistry : (Print), (2000), 43(3), 369-380, 16 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000081959690060
UP 20001101

AB A new generation of cyclic **matrix metalloproteinase** (**MMP**) inhibitors derived from dl-piperazinecarboxylic acid has been described. The design involves: incorporation of **hydroxamic** acid as the bidentate chelating agent for catalytic Zn.sup.2.sup.+, placement of a sulfonamide group at the 1N-position of the piperazine ring to fill the S1' pocket of the enzyme, and finally attachment of diverse functional groups at the 4N-position to optimize potency and peroral absorption. A unique combination of all three elements produced

inhibitor 20 with high affinity for **MMPs** 1, 3, 9, and 13 (24, 18, 1.9, and 1.3 nM, respectively). X-ray crystallography data obtained for **MMP**-3 cocrystallized with 20 gave detailed information on key binding interactions defining an overall scaffold geometry for piperazine-based **MMP** inhibitors.

L51 ANSWER 73 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999-0369021 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Picking the S.sub.1, S.sub.1' and S.sub.2' pockets of **matrix metalloproteinases.** A niche for potent acyclic sulfonamide inhibitors
AUTHOR: HANESSIAN S.; BOUZBOUZ S.; BOUDON A.; TUCKER G. C.; PEYROULAN D.
CORPORATE SOURCE: Department of Chemistry, Universite de Montreal, C.P. 6128, Succursale Centre-ville, Montreal, Quebec, H3C 3J7, Canada
SOURCE: Bioorganic & medicinal chemistry letters, (1999), 9(12), 1691-1696, 27 refs.
ISSN: 0960-894X
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-22446, 354000085436970140
UP 20001101
AB A series of acyclic **hydroxamic** acids harboring strategically placed α-arylsulfonamido and thioether groups was synthesized and found to be potent inhibitors of various **MMPs.** An unprecedented cleavage of t-butyl **hydroxamates** to **hydroxamic** acids was found.

L51 ANSWER 74 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999-0217063 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Dual inhibition of phosphodiesterase 4 and **matrix metalloproteinases** by an (arylsulfonyl)**hydroxamic** acid template
AUTHOR: GRONEBERG R. D.; BURNS C. J.; MORRISSETTE M. M.; ULLRICH J. W.; MORRIS R. L.; DARNBROUGH S.; DJURIC S. W.; CONDON S. M.; MCGEEHAN G. M.; LABAUDINIERE R.; NEUENSCHWANDER K.; SCOTESE A. C.; KLINE J. A.
CORPORATE SOURCE: Rhone-Poulenc Rorer, SW8, 500 Arcola Road, Collegeville, Pennsylvania 19426, United States
SOURCE: Journal of medicinal chemistry, (1999), 42(4), 541-544, 26 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal; (letter to editor)
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000074385190030
UP 20001101

L51 ANSWER 75 OF 85 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998-0119306 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1998 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Striking effect of **hydroxamic** acid substitution on the phosphodiesterase type 4 (PDE4) and **TNF**.alpha. inhibitory activity of two series of rolipram analogues : Implications for a new active site model of PDE4
AUTHOR: KLEINMAN E. F.; CAMPBELL E.; GIORDANO L. A.; COHAN V. L.; JENKINSON T. H.; CHENG J. B.; SHIRLEY J. T.; PETTIPHER E. R.; SALTER E. D.; HIBBS T. A.; DICAPUA F. M.; BORDNER J.
CORPORATE SOURCE: Central Research Division, Pfizer Inc., Groton, Connecticut 06340, United States
SOURCE: Journal of medicinal chemistry, (1998), 41(3), 266-270, 20 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal; (letter to editor)
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000077888630020
UP 20001101

L51 ANSWER 76 OF 85 CANCERLIT on STN
ACCESSION NUMBER: 97302628 CANCERLIT
DOCUMENT NUMBER: 97302628 PubMed ID: 9158875
TITLE: Synthesis and biological evaluation of orally active **matrix metalloproteinase** inhibitors.
AUTHOR: Hirayama R; Yamamoto M; Tsukida T; Matsuo K; Obata Y; Sakamoto F; Ikeda S
CORPORATE SOURCE: New Drug Discovery Research Laboratory, Osaka, Japan.
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY, (1997 Apr) 5 (4) 765-78.
Journal code: 9413298. ISSN: 0968-0896.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 97302628
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970909
Last Updated on STN: 19970909
ED Entered STN: 19970909
Last Updated on STN: 19970909
AB The synthesis and biological evaluation of orally active inhibitors of **matrix metalloproteinase** are reported. Modifications of the P2' position and the alpha-substituent of **hydroxamic** acid derivatives were carried out, and revealed that the P2' substituent influenced the **MMP** inhibitory activities in vitro and in plasma after oral administration. The **hydroxamates** with **phenylglycine** at the P2' position were absorbed well orally. Compound 15e, which exhibited the longest duration of inhibitory activity in plasma after oral administration among the phenylglycine derivatives (5a-5d, 15a, 15c, 15e), was evaluated in a rat adjuvant arthritis model. A reduction in hind foot pad swelling and improvements of some inflammatory parameters were demonstrated when the compound was administered orally. These results indicate the potential of **MMP** inhibitors for rheumatoid arthritis.
CT Check Tags: Animal; Human; Male

Absorption
Administration, Oral
*Anti-Inflammatory Agents: CS, chemical synthesis
Anti-Inflammatory Agents: PK, pharmacokinetics
Anti-Inflammatory Agents: TU, therapeutic use
*Arthritis, Experimental: DT, drug therapy
Biological Availability
Collagenases: AI, antagonists & inhibitors
Collagenases: BL, blood
Disease Models, Animal
Gelatinases: AI, antagonists & inhibitors
Gelatinases: BL, blood
Hindlimb: DE, drug effects
Hydroxamic Acids: CH, chemistry
*Metalloendopeptidases: AI, antagonists & inhibitors
Mice
*Protease Inhibitors: CS, chemical synthesis
Protease Inhibitors: PK, pharmacokinetics
Protease Inhibitors: TU, therapeutic use
Rats
Rats, Inbred Lew
Solubility
Structure-Activity Relationship
Tumor Cells, Cultured
CN 0 (Anti-Inflammatory Agents); 0 (Hydroxamic Acids); 0 (Protease Inhibitors); EC 3.4.24 (Metalloendopeptidases); EC 3.4.24.- (Collagenases); EC 3.4.24.- (Gelatinases)

L51 ANSWER 77 OF 85 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-35901 DRUGU C P B
TITLE: Novel 4-substituted **phenylsulfanyl** alkyl and aryl **hydroxamic** acid **TACE** and **MMP** inhibitors.
AUTHOR: Davis J M; Venkatesan A; Baker J L; Grosu G T; Ellingboe J W; Zask A; Skotnicki J; Killar L; Cowling R; Jin G
CORPORATE SOURCE: Wyeth-Ayerst
LOCATION: Pearl River, N.Y., USA
SOURCE: Abstr.Pap.Am.Chem.Soc. (219 Meet., Pt. 2, MEDI 281, 2000) 1 Fig.
CODEN: ACSRAL ISSN: 0065-7727
AVAIL. OF DOC.: Chemical Sciences, Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, U.S.A. (email: davisjm@war.wyeth.com). (12 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB **Tumor necrosis** factor **alpha** (TNFa) **converting** enzyme (**TACE**) plays a key role in the release of TNFa, a cytokine involved in inflammation, from cells. Unregulated, this can lead to several pathological conditions including rheumatoid arthritis. Several sulfanyl **hydroxamic** acids of structure (I) were synthesized and evaluated for inhibition of **TACE** and the related **matrix metalloproteinase** (**MMP**) 1, 9 and 13 in-vitro. No further details are given. (conference abstract: 219th ACS National Meeting, San Francisco, California, USA, 2000).

L51 ANSWER 78 OF 85 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-02274 DRUGU C P B

TITLE: **Hydroxamate** derivatives of substrate-analogous peptides containing aminomalonic acid are potent inhibitors of **matrix metalloproteinases.**
AUTHOR: Krumme D; Wenzel H; Tschesche H
CORPORATE SOURCE: Univ.Bielefeld
LOCATION: Bielefeld, Ger.
SOURCE: FEBS Lett. (436, No. 2, 209-12, 1998) 1 Fig. 1 Tab. 16 Ref.
CODEN: FEBLAL ISSN: 0014-5793
AVAIL. OF DOC.: Universitaet Bielefeld, Fakultaet fuer Chemie, Abteilung Biochemie I, Universitaetsstrasse 25, D-33615 Bielefeld, Germany. (H.T.). (e-mail: harald.tschesche@uni-bielefeld.de).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Tetrapeptides Boc-Pro-Aaa-Ama(NHOH)-Tyr(Bzl)-R2 were prepared, where Aaa = Gly, Ala or Leu, Ama(NHOH) = aminomalonic acid **hydroxamate**, Tyr(Bzl) = O-**benzyl**-Tyr, and R2 = bulky amine. Peptides were tested as **matrix metalloproteinase** (**MMP**) human gelatinase-B (**MMP**-9) inhibitors. Analogs had **MMP**-9 selectivity and were weak inhibitors of the catalytic domain of neutrophil elastase (cdMMP-8). The peptides resisted proteinase cleavage. Substrate was (7-methoxycoumarin-4-yl)acetyl Pro-Leu-Gly-Leu (3-(2,4-dinitrophenyl) L-2,3-diaminopropionyl)-Ala-Arg-NH2 which was cleaved at the Gly-Leu bond by both cdMMP-8 and **MMP**-9.

L51 ANSWER 79 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:432055 SCISEARCH
THE GENUINE ARTICLE: 916HS
TITLE: Conformational variability of **matrix metalloproteinases**: Beyond a single 3D structure
AUTHOR: Bertini I (Reprint); Calderone V; Cosenza M; Fragai M; Lee Y M; Luchinat C; Mangani S; Terni B; Turano P
CORPORATE SOURCE: Univ Florence, Magnet Resonance Ctr, Via Luigi Sacconi 6, I-50019 Sesto Fiorentino, Italy (Reprint); Univ Florence, Magnet Resonance Ctr, I-50019 Sesto Fiorentino, Italy; Univ Florence, Dept Chem, I-50019 Sesto Fiorentino, Italy; Univ Siena, Dept Chem, I-53100 Siena, Italy; Univ Florence, Dept Agr Biotechnol, I-50144 Florence, Italy
bertini@cerm.unifi.it
COUNTRY OF AUTHOR: Italy
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (12 APR 2005) Vol. 102, No. 15, pp. 5334-5339.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34
ENTRY DATE: Entered STN: 28 Apr 2005
Last Updated on STN: 28 Apr 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 28 Apr 2005
Last Updated on STN: 28 Apr 2005
AB The structures of the catalytic domain of **matrix metalloproteinase** 12 in the presence of **acetohydroxamic** acid and N-isobutyl-N-[4-**methoxyphenylsulfonyl**]glycyl **hydroxamic** acid have been solved by x-ray diffraction in the

crystalline state at 1.0 and 1.3-angstrom resolution, respectively, and compared with the previously published x-ray structure at 1.2-angstrom resolution of the adduct with batimastat. The structure of the N-isobutyl-N-[4-**methoxyphenylsulfonyl**]glycyl **hydroxamic** acid adduct has been solved by NMR in solution. The three x-ray structures and the solution structure are similar but not identical to one another, the differences being sizably higher in the loops. We propose that many of the loops show a dynamical behavior in solution on a variety of time scales. Different conformations of some flexible regions of the protein can be observed as "frozen" in different crystalline environments. The mobility in solution studied by NMR reveals conformational equilibria in accessible time scales, i.e., from 10(-5) s toms and more. Averaging of some residual dipolar couplings is consistent with further motions down to 10(-9) s. Finally, local thermal motions of each frozen conformation in the crystalline state at 100 K correlate well with local motions on the picosecond time scale. Flexibility/conformational heterogeneity in crucial parts of the catalytic domain is a rule rather than an exception in **matrix metalloproteinases**, and its extent may be underestimated by inspection of one x-ray structure. Backbone flexibility may play a role in the difficulties encountered in the design of selective inhibitors, whereas it may be a requisite for substrate binding and broad substrate specificity.

L51 ANSWER 80 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:525729 SCISEARCH
THE GENUINE ARTICLE: 927OU
TITLE: Synthesis, radiosynthesis, in vitro and preliminary in vivo evaluation of **biphenyl** carboxylic and **hydroxamic matrix metalloproteinase** (**MMP**) inhibitors as potential tumor imaging agents
AUTHOR: Oltenfreiter R (Reprint); Staelens L; Hillaert U; Heremans A; Noel A; Frankenne F; Slegers G
CORPORATE SOURCE: State Univ Ghent, Lab Radiopharm, Harelbekestr 72, B-9000 Ghent, Belgium (Reprint); State Univ Ghent, Lab Radiopharm, B-9000 Ghent, Belgium; Univ Liege, Lab Tumor & Dev Biol, Liege, Belgium; State Univ Ghent, Med Chem Lab, B-9000 Ghent, Belgium
ruth.oltenfreiter@ugent.be
COUNTRY OF AUTHOR: Belgium
SOURCE: APPLIED RADIATION AND ISOTOPES,C(JUN 2005) Vol. 62, No. 6, pp. 903-913.
ISSN: 0969-8043.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 30
ENTRY DATE: Entered STN: 2 Jun 2005
Last Updated on STN: 2 Jun 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 2 Jun 2005
Last Updated on STN: 2 Jun 2005

AB Excess matrix degradation is one of the hallmarks of cancer and is an important factor in the process of tumor progression. It is implicated in invasion, metastasis, growth, angiogenesis and migration. Many characteristics of matrix metaloproteinases (**MMPs**) make them attractive therapeutic and diagnostic targets. **MMP** expression is upregulated at the tumor site, with localization of activity in the

tumor or the surrounding stroma, providing a target for medical imaging techniques. Radioiodinated carboxylic and **hydroxamic** **MMP** inhibitors 2-(4'-[(123I)] iodo-**biphenyl** -4sulfonylamino)-3-methyl-butyric acid (9) and 2-(4'-[I-123] iodo-biphenyl-4-sulfonylamino)-3-methyl-butyramide (11), their unlabelled standards and precursors were synthesized. Radioiodination was conducted by electrophilic aromatic osubstitution of the tributylstannyl precursors and resulted in radiochemical yields of 70 +/- 5% (n = 6) and 60 + 5% (n = 4), respectively. In vitro zymography and enzyme assays showed for both **hydroxamic** acid and carboxylic acid compounds a good inhibition activity and a high selectivity for **MMP**-2. In vivo biodistribution in NMRI mice showed no long-term accumulation in organs and the possibility to accumulate in the tumor in a later phase of this study. (c) 2005 Elsevier Ltd. All rights reserved.

L51 ANSWER 81 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:960039 SCISEARCH
THE GENUINE ARTICLE: 737PA
TITLE: Iminodiacetyl-**hydroxamate** derivatives as metalloproteinase inhibitors: equilibrium complexation studies with Cu(II), Zn(II) and Ni(II)
AUTHOR: Chaves S; Marques S; Santos M A (Reprint)
CORPORATE SOURCE: Inst Super Tecn, Ctr Quim Estrutural, Complexo 1, Av Rovisco Pais, P-1049001 Lisbon, Portugal (Reprint); Inst Super Tecn, Ctr Quim Estrutural, P-1049001 Lisbon, Portugal
COUNTRY OF AUTHOR: Portugal
SOURCE: JOURNAL OF INORGANIC BIOCHEMISTRY, (1 DEC 2003) Vol. 97, No. 4, pp. 345-353.
ISSN: 0162-0134.
PUBLISHER: ELSEVIER SCIENCE INC, 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 48
ENTRY DATE: Entered STN: 14 Nov 2003
Last Updated on STN: 14 Nov 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 14 Nov 2003
Last Updated on STN: 14 Nov 2003

AB Two new iminodiacetyl-**hydroxamate** derivatives, the N-**benzyl**-N-carboxymethyl-**iminoacetohydroxamic** acid (H2L1) and the N-**benzyl**-N'-hydroxypiperazine-2,6-dione (HL2), have been recently reported as very effective inhibitors against a set of zinc-containing **matrix metalloproteinases** (**MMPs**). Herein, aimed at understanding that inhibitory function, these compounds are studied in their complex formation equilibria with three biologically relevant first-row transition M2+ metal ions (M=Cu, Zn, Ni) by using potentiometric and spectroscopic techniques. At physiological conditions, complexation of these metal ions by H2L1 mostly occurs with formation of 1:1 species by tridentate co-ordination (O,N,N) (carboxylate-amino-**hydroxamate**), whereas complexation with HL2 mainly involves the formation of 1:2 (M:L) species with normal (O,O) **hydroxamate** coordination. Moreover, at higher pH, H2L1 is able to form a pentanuclear tetrameric copper complex with an interesting 12-metallacrown-4 structure. (C) 2003 Elsevier Inc. All rights reserved.

L51 ANSWER 82 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:55980 SCISEARCH
THE GENUINE ARTICLE: 508KZ
TITLE: **Phenoxyphenyl** sulfone N-formylhydroxylamines (**retrohydroxamates**) as potent, selective, orally bioavailable **matrix metalloproteinase** inhibitors
AUTHOR: Wada C K (Reprint); Holms J H; Curtin M L; Dai Y; Florjancic A S; Garland R B; Guo Y; Heyman H R; Stacey J R; Steinman D H; Albert D H; Bouska J J; Elmore I N; Goodfellow C L; Marcotte P A; Tapang P; Morgan D W; Michaelides M R; Davidsen S K
CORPORATE SOURCE: Abbott Labs, Canc Res Area, Dept 47J, Bldg AP10, 100 Abbott Pk Rd, Abbott Pk, IL 60064 USA (Reprint); Abbott Labs, Canc Res Area, Dept 47J, Abbott Pk, IL 60064 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (3 JAN 2002) Vol. 45, No. 1, pp. 219-232.
ISSN: 0022-2623.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 25 Jan 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 25 Jan 2002
Last Updated on STN: 25 Jan 2002

AB A novel series of sulfone N-formylhydroxylamines (**retrohydroxamates**) have been investigated as **matrix metalloproteinases** (**MMP**) inhibitors. The substitution of the ether linkage of ABT-770 (5) with a sulfone group 13a led to a substantial increase in activity against **MMP**-9 but was accompanied by a loss of selectivity for inhibition of **MMP**-2 and -9 over **MMP**-1 and diminished oral exposure. Replacement of the biphenyl P1' substituent with a phenoxyphenyl group provided compounds that are highly selective for inhibition of **MMP**-2 and -9 over **MMP**-1. Optimization of the substituent adjacent to the **retrohydroxamate** center in this series led to the clinical candidate ABT-518 (6), a highly potent, selective, orally bioavailable **MMP** inhibitor that has been shown to significantly inhibit tumor growth in animal cancer models.

L51 ANSWER 83 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:290351 SCISEARCH
THE GENUINE ARTICLE: 302XH
TITLE: Protease inhibitors - Part 5. Alkyl/arylsulfonyl- and arylsulfonylureido-/arylureido- glycine **hydroxamate** inhibitors of Clostridium histolyticum collagenase
AUTHOR: Scozzafava A; Supuran C T (Reprint)
CORPORATE SOURCE: Univ Florence, Lab Chim Inorgan & Bioinorgan, Via Gino Capponi 7, I-50121 Florence, Italy (Reprint); Univ Florence, Lab Chim Inorgan & Bioinorgan, I-50121 Florence, Italy
COUNTRY OF AUTHOR: Italy
SOURCE: EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, (MAR 2000) Vol. 35, No. 3, pp. 299-307.
ISSN: 0223-5234.

PUBLISHER: EDITIONS SCIENTIFIQUES MEDICALES ELSEVIER, 23 RUE LINOIS, 75724 PARIS CEDEX 15, FRANCE.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 49
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 2000
Last Updated on STN: 2000

AB Reaction of alkyl/arylsulfonyl halides with glycine afforded a series of derivatives which were first N-benzylated by treatment with **benzyl** chloride, and then converted to the corresponding **hydroxamic** acids with hydroxylamine in the presence of carbodiimide derivatives. Other derivatives were obtained by reaction of N-benzyl-glycine with aryl isocyanates, arylsulfonyl isocyanates or benzoyl isothiocyanate, followed by conversion of their COOH group into the CONHOH moiety, as mentioned above. The 90 new compounds reported here were assayed as inhibitors of the Clostridium histolyticum collagenase (EC 3.4.24.3), a zinc enzyme which degrades triple helical regions of native collagen. The prepared **hydroxamate** derivatives were generally 100-500 times more active than the corresponding carboxylates. In the series of synthesized **hydroxamates**, substitution patterns leading to the best inhibitors were those involving perfluoroalkylsulfonyl- and substituted-arylsulfonyl moieties, such as pentafluorophenylsulfonyl, 3- and 4-carboxyphenylsulfonyl-, 3-trifluoromethyl-phenylsulfonyl or 1- and 2-naphthyl among others. Thus, it seems that similarly to the **matrix metalloproteinase** (**MMP**) **hydroxamate** inhibitors, Clostridium histolyticum collagenase inhibitors should incorporate hydrophobic moieties at the P-1- and P-2- sites, whereas the alpha-carbon substituent may be a small and compact moiety (such as H, for the Gly derivatives reported here). Such compounds might lead to the design of collagenase inhibitor-based drugs useful as anti-cancer, anti-arthritis or anti-bacterial agents for the treatment of corneal keratitis. (C) 2000 Editions scientifiques et medicales Elsevier SAS.

L51 ANSWER 84 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:749562 SCISEARCH
THE GENUINE ARTICLE: 317UW
TITLE: Novel 4-substituted **phenylsulfanyl** alkyl and aryl **hydroxamic** acid **TACE** and **MMP** inhibitors.
AUTHOR: Davis J M (Reprint); Venkatesan A; Baker J L; Grosu G T; Ellingboe J W; Zask A; Skotnicki J; Killar L; Cowling R; Jin G X; Sharr M; Sung A
CORPORATE SOURCE: Wyeth Ayerst Res, Chem Sci, Pearl River, NY 10965 USA; Wyeth Ayerst Res, Oncol Immunoinflammatory Dis, Pearl River, NY 10965 USA
COUNTRY OF AUTHOR: USA
SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (26 MAR 2000) Vol. 219, Part 2, pp. U52-U52. MA 281-MEDI. ISSN: 0065-7727.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 2000

Last Updated on STN: 2000
ED Entered STN: 2000
Last Updated on STN: 2000

L51 ANSWER 85 OF 85 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:682758 SCISEARCH
THE GENUINE ARTICLE: 232MG
TITLE: Arylsulphonamide **hydroxamic** acids as potent inhibitors of **MMP**-13
AUTHOR: ANON
SOURCE: EXPERT OPINION ON THERAPEUTIC PATENTS, (SEP 1999) Vol. 9, No. 9, pp. 1303-1307.
ISSN: 1354-3776.
PUBLISHER: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 1999
Last Updated on STN: 1999
AB Pfizer has disclosed a series of **phenoxyphenyl** sulphonamide **hydroxamic** acids, containing Ca gem-disubstitution and a novel N-ethylcarboxylate moiety, which are potent inhibitors of **matrix metalloproteinase**-13 (**MMP**-13), an enzyme which has been implicated in such disease states as cancer and arthritis. The compounds are significantly selective (300-1000 fold) for **MMP**-13 versus **MMP**-1, the inhibition of which is believed to be associated with clinical side effects with previous broad spectrum **MMP** inhibitors. The Pfizer compounds are equally or more selective than several current clinical candidates and may have favourable pharmacodynamic profiles.

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=> d his l50

     (FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA,
     CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT
     08:28:53 ON 13 OCT 2005)
L50          10 DUP REM L49 (3 DUPLICATES REMOVED)

=> d que l50
L1              QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L48         147 SEA MADUSKUIE, T?/AU
L49          13 SEA L48 AND L1
L50          10 DUP REM L49 (3 DUPLICATES REMOVED)


=> d ibib ed ab l50 1-10
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, DRUGU, SCISEARCH' - CONTINUE?
(Y)/N:y



L50  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:120672  HCAPLUS
DOCUMENT NUMBER:          140:177322
TITLE:                    Hydroxamic acid derivative inhibitors of
                          matrix metalloproteinases and/or TNFα converting
                          enzyme for use in treatment of diseases
INVENTOR(S):              Maduskuie, Thomas P.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 81 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004012663         A2    20040212    WO 2003-US23989         20030731
     WO 2004012663         A3    20040708
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004063698         A1    20040401    US 2003-632197          20030731
PRIORITY APPLN. INFO.:                     US 2002-400237P      P  20020801
OTHER SOURCE(S):          MARPAT 140:177322
ED   Entered STN:  13 Feb 2004
AB   MMP or TACE-inhibiting hydroxamic acid derivs. for use in
     treatment of diseases are disclosed.  Thus, 3,N-dihydroxy-2,2-dimethyl-3-
     [6-(2-methylquinolin-4-ylmethoxy)naphthalen-2-yl]propionamide (I),
     4,N-dihydroxy-4-[4-(2-methylquinolin-4-ylmethoxy)phenyl]butyramide (II),
     N-Hydroxy-2-{2-[4-(2-methylquinolin-4-ylmethoxy)phenyl]tetrahydrofuran-2-
     yl}acetamide (III), and 3,N-dihydroxy-3-(6-methoxynaphthalen-2-yl)-2,2-
     dimethylpropionamide (IV) as well as 23 other compds. were synthesized and
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tested as MMP inhibitors. Some of these compds. inhibited MMPs with Ki's ≤ 10 μM.

L50 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:634809 HCAPLUS
TITLE: Design, synthesis and evaluation of β-amino **hydroxamic** acids as selective tumor necrosis factor-α converting enzyme inhibitors
AUTHOR(S): Duan, James J.-W.; Ott, Gregory R.; King, Bryan W.; **Maduskuie, Thomas P.**; Xue, Chu-Biao; Chen, Lihua; Lu, Zhonghui; Gilmore, John L.; Asakawa, Naoyuki; Mercer, Stephen E.; Xu, Meizhong; Harris, Cathy M.; Wasserman, Zelda R.; Liu, Rui-Qin; Covington, Maryanne B.; Qian, Mingxin; Vaddi, Krishna G.; Christ, David D.; Hardman, Karl D.; Ribadeneira, Maria D.; Newton, Robert C.; Trzaskos, James M.; Decicco, Carl P.
CORPORATE SOURCE: Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-201. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
ED Entered STN: 15 Aug 2003
AB Tumor necrosis factor-α converting enzyme (TACE) is the principal metalloprotease that processes the pro-form of tumor necrosis factor-α (TNFα) to the soluble form. With the clin. success of anti-TNFα biologics in diseases such as rheumatoid arthritis, TACE has attracted significant interest as an intervention point for small mols. to suppress the amount of circulating TNFα. Most of the early TACE inhibitors were derived from inhibitors of structurally related matrix metalloproteinases (MMPs) and hence suffered from lack of TACE selectivity. In an effort to discover selective TACE inhibitors, a series of β-amino **hydroxamates** was found to be highly potent and selective for TACE relative to MMPs. The design, synthesis and evaluation of these inhibitors will be presented.

L50 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:117029 HCAPLUS
DOCUMENT NUMBER: 132:166134
TITLE: Preparation of succinoylaminoazepinones and related compounds as inhibitors of Aβ-peptide production.
INVENTOR(S): Olson, Richard E.; **Maduskuie, Thomas P.**; Thomas, Lorin Andrew
PATENT ASSIGNEE(S): Du Pont Pharmaceuticals Co., USA
SOURCE: PCT Int. Appl., 315 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000007995	A1	20000217	WO 1999-US17717	19990807

W: AL, AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MK, MX,

NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

HR 990246	A1	20000630	HR 1999-990246		19990806
CA 2338944	AA	20000217	CA 1999-2338944		19990807
AU 9953378	A1	20000228	AU 1999-53378		19990807
AU 756830	B2	20030123			
EP 1102752	A1	20010530	EP 1999-939010		19990807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200100377	T2	20010621	TR 2001-200100377		19990807
BR 9912969	A	20010925	BR 1999-12969		19990807
NZ 509241	A	20030829	NZ 1999-509241		19990807
JP 2003526603	T2	20030909	JP 2000-563629		19990807
NZ 525513	A	20040924	NZ 1999-525513		19990807
PRIORITY APPLN. INFO.:			US 1998-95698P	P	19980807
			US 1998-113558P	P	19981224
			US 1999-120227P	P	19990215
			US 1999-370089	A	19990806
			US 1998-113588P	P	19981224
			WO 1999-US17717	W	19990807

OTHER SOURCE(S): MARPAT 132:166134
ED Entered STN: 18 Feb 2000
AB Title compds. [I; Q = OR1, NR1R2; R1 = H, (substituted) alkyl, alkenyl, carbocyclyl, aryl, heterocyclyl; R2 = H, NH2, OH, alkyl, alkoxy, PhO, PhCH2O, carbocyclyl, aryl, heterocyclyl; R3 = (CR7R7a)nR4, etc.; n = 0-3; R3a = H, OH, alkyl, alkoxy, alkenyloxy; R4 = H, OH, (substituted) alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl; R5 = H, OR14, (substituted) alkyl, alkoxy, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl; R14 = H, Ph, PhCH2, alkyl, alkoxyalkyl; R5a = H, OH, alkyl, alkoxy, alkenyl, alkenyloxy; R6 = H, (substituted) alkyl, carbocyclyl, aryl; R7, R7a = H, OH, Cl, F, Br, iodo, cyano, NO2, CF3, alkyl; W = (CR8R8a)p; p = 0-4; R8, R8a = H, F, alkyl, alkenyl, alkynyl, cycloalkyl; X = bond, (substituted) aryl, carbocyclyl, heterocyclyl; Y = bond, (CR9R9a)tV(CR9R9a)u; t, u = 0-3; R9, R9a = H, F, alkyl, cycloalkyl; V = bond, CO, O, S, SO, SO2, imino, etc.; Z = (substituted) alkyl, aryl, carbocyclyl, heterocyclyl; B = atoms to form an (unsatd.) (substituted) (heteroatom-containing) lactam ring], were prepared which inhibit the processing of amyloid precursor protein and, more specifically, inhibit the production of Aβ-peptide, thereby acting to prevent the formation of neurol. deposits of amyloid protein. Thus, title compound (II) was prepared in several steps starting with L-α-amino-ε-caprolactam. I inhibited Aβ production with IC50<100 μM.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739801 HCAPLUS
TITLE: Synthesis and structure-activity relationship of a novel, achiral series of TNF-alpha converting enzyme inhibitors
AUTHOR(S): Gilmore, John L.; King, Bryan W.; Harris, Cathy; **Maduskuie, Thomas P.**; Mercer, Stephen E.; Liu, Rui Quin; Covington, Maryanne B.; Qian, Mingxin; Ribadeneria, Maria D.; Vaddi, Krishna G.; Trzaskos, James M.; Newton, Robert C.; Decicco, Carl P.; Duan, James J.-W.
CORPORATE SOURCE: Discovery Chemistry, Bristol-Myers Squibb

Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-290. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
ED Entered STN: 12 Aug 2005
AB TNF-alpha is a potent proinflammatory cytokine which when disregulated has been implicated in chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. The marketed anti-TNF biologics, Enbrel, Remicade, and Humira are effective in the treatment of these diseases by sequestering the soluble form of TNF- alpha. An alternate approach is to inhibit the release of soluble TNF- alpha via proteinase inhibitors such as TNF- alpha Converting Enzyme (TACE). We have discovered a novel, achiral series of compds. which are effective in inhibiting TACE. The synthesis and biol. activity of these beta, beta -cyclic beta-**amidohydroxamic** acids will be presented.

L50 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:772797 HCAPLUS
DOCUMENT NUMBER: 141:261062
TITLE: Preparation of (succinoylamino)azepinones as inhibitors of Aβ protein
INVENTOR(S): Olson, Richard E.; **Maduskuie, Thomas P.**; Thompson, Lorin Andrew
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S., 101 pp., Cont.-in-part of U.S. Ser. No. 370,089.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6794381	B1	20040921	US 2000-506360		20000217
HR 990246	A1	20000630	HR 1999-990246		19990806
TR 200100377	T2	20010621	TR 2001-200100377		19990807
NZ 525513	A	20040924	NZ 1999-525513		19990807
US 2003134841	A1	20030717	US 2002-285776		20021101
PRIORITY APPLN. INFO.:			US 1998-95698P	P	19980807
			US 1998-113558P	P	19981224
			US 1999-120227P	P	19990215
			US 1999-370089	A2	19990806
			US 2000-506360	A3	20000217

OTHER SOURCE(S): MARPAT 141:261062
ED Entered STN: 22 Sep 2004
AB The invention relates to aminoazepinones I [R1 = H, (un)substituted alkyl, alkenyl, carbocyclyl, aryl or heterocyclyl; R2 = H or alkyl; R3 = (un)substituted (hetero)alkyl; R3a = H, OH, alkyl, alkoxy, alkenyloxy; R5 = H, OH, (un)substituted alkyl, alkoxy, alkenyl, alkynyl, carbocyclyl, aryl or heterocyclyl; R5a = H, OH, alkyl, alkoxy, alkenyl, alkenyloxy; R6 = H, (un)substituted alkyl, carbocyclyl or aryl; W = bond or (un)substituted alkylene; X = bond, (un)substituted aryl, carbocyclyl or heterocyclyl; Y = bond or (un)substituted (hetero)alkylene; Z = (un)substituted alkyl, aryl, carbocyclyl or heterocyclyl; B = atoms to form a saturated or unsatd. seven-membered ring which may be substituted]

which inhibit the processing of Aβ-peptide, thereby acting to prevent the formation of neurol. deposits of amyloid protein. More particularly, the invention relates to the treatment of neurol. disorders related to β-amyloid production such as Alzheimer's disease and Down's Syndrome. Thus, aminoazepinone II was prepared in several steps starting with L-α-amino-ε-caprolactam. I inhibited Aβ production with IC50 < 100 μM.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:444499 HCAPLUS
DOCUMENT NUMBER: 137:33207
TITLE: Preparation of novel N-substituted-γ,γ-trisubstituted lactam derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Duan, Jingwu; DeCicco, Carl P.; Wasserman, Zelda R.; **Maduskuie, Thomas P., Jr.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 119 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403632	B1	20020611	US 2000-516709	20000301
US 2003134827	A1	20030717	US 2002-96619	20020312
US 6610731	B2	20030826		
PRIORITY APPLN. INFO.:			US 1997-62418P	P 19971003
			US 1998-165747	A3 19981002
			US 2000-516709	A3 20000301

OTHER SOURCE(S): MARPAT 137:33207
ED Entered STN: 13 Jun 2002
AB Title compds. [I; A is selected from COOH, CH2COOH, CONHOH, SH, CH2SH, PO(OH)2, etc.; ring B is a 4-8 membered cyclic amide containing 0-3 heteroatoms from O, N, and S, etc.; R1 is phenylmethoxyphenyl, phenoxyphenyl, etc.; R2 is H, CH3, Et, i-Pr, etc.; R1-R2 combine to form heterocyclic; R3 is H, alkylene, heterocyclic, etc.; R4 is H, alkylene, etc.; R3-R4 combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepared as useful metalloprotease inhibitors. For instance, 4-benzyloxyphenyl acetate was sequentially alkylated (THF, NaHMDS) with MeI and allyl bromide to afford the α,α-bis(alkylated) derivative which was converted to the aldehyde (CH2Cl2, O3) and was subsequently reacted with D-alanine Me ester hydrochloride and Zn° in HOAc to yield the lactam ester. This intermediate was treated with hydroxylamine to give **hydroxamic** acid II.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:2000 BIOSIS
DOCUMENT NUMBER: PREV200400003348
TITLE: Design, synthesis and evaluation of beta-amino **hydroxamic** acids as selective tumor necrosis factor-alpha converting enzyme inhibitors.
AUTHOR(S): Duan, James J.-W. [Reprint Author]; Ott, Gregory R.

[Reprint Author]; King, Bryan W. [Reprint Author]; **Maduskuie, Thomas P.** [Reprint Author]; Xue, Chu-Biao [Reprint Author]; Chen, Lihua [Reprint Author]; Lu, Zhonghui [Reprint Author]; Gilmore, John L. [Reprint Author]; Asakawa, Naoyuki [Reprint Author]; Mercer, Stephen E. [Reprint Author]; Xu, Meizhong [Reprint Author]; Harris, Cathy M. [Reprint Author]; Wasserman, Zelda R. [Reprint Author]; Liu, Rui-Qin [Reprint Author]; Covington, Maryanne B. [Reprint Author]; Qian, MingXin [Reprint Author]; Vaddi, Krishna G. [Reprint Author]; Christ, David D. [Reprint Author]; Hardman, Karl D. [Reprint Author]; Ribadeneira, Maria D. [Reprint Author]; Newton, Robert C. [Reprint Author]; Trzaskos, James M. [Reprint Author]; Decicco, Carl P. [Reprint Author]

CORPORATE SOURCE: Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ, 08543-4000, USA
james.duan@bms.com

SOURCE: Abstracts of Papers American Chemical Society, (2003) Vol. 226, No. 1-2, pp. MEDI 201. print.
Meeting Info.: 226th ACS (American Chemical Society) National Meeting. New York, NY, USA. September 07-11, 2003. American Chemical Society.
ISSN: 0065-7727 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 17 Dec 2003
Last Updated on STN: 17 Dec 2003

ED Entered STN: 17 Dec 2003
Last Updated on STN: 17 Dec 2003

L50 ANSWER 8 OF 10 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1995-12212 DRUGU C P B

TITLE: Acyl CoA: Cholesterol acyltransferase (ACAT) inhibitors: ureas bearing heterocyclic groups biosteric for an imidazole.

AUTHOR: Wilde R G; Billheimer J T; Germain S J; Gillies P J; Higley C A; Kezar H S III; **Maduskuie T P**; Shimshick E S; Wexler R R

CORPORATE SOURCE: Du-Pont; Merck-USA
LOCATION: Wilmington, Del., USA

SOURCE: ; Bioorg.Med.Chem.Lett. (5, No. 2, 167-72, 1995) 4 Fig. 3 Tab. 10 Ref.
CODEN: ; BMCL

AVAIL. OF DOC.: Cardiovascular Diseases Research, Division of Research and Development, The DuPont Merck Pharmaceutical Company, DuPont Experimental Station, Wilmington, Delaware, U.S.A. 19880-0353.

LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB A series of compounds (1-34) bearing heterocyclic substituents was synthesized and evaluated in-vitro for inhibition of acyl CoA: cholesterol acyltransferase (ACAT) using two assays (one based on the determination of the formation of labeled cholesteryl oleate in the presence of rat hepatic microsomes; the second was based on the measurement of the formation of cholesteryl ester (CE) by following the rate of oleate incorporation into CE). Results obtained indicated that for five-membered rings fused to another ring, the most potent inhibitors

of ACAT were imidazoles. Oxazoles, thiazoles and N-substituted imidazoles were less potent. Triazoles were also less potent, but the **hydantoin** compound (33) was within one order of magnitude of DuP 128. From results of QSAR, extremely hydrophilic heterocycles were expected to decrease potency.

L50 ANSWER 9 OF 10 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1989-22660 DRUGU C P
TITLE: Hydroxyacetophenone- Derived Antagonists of the Peptidoleukotrienes.
AUTHOR: Brown F J; Bernstein P R; Cronk L A; Dosset D L; Hebbel K C; **Maduskuie T P**
CORPORATE SOURCE: ICI-Americas
LOCATION: Wilmington, Delaware, United States
SOURCE: J.Med.Chem. (32, No. 4, 807-26, 1989) 9 Tab. 50 Ref.
CODEN: JMCMAR ISSN: 0022-2623
AVAIL. OF DOC.: Department of Medicinal Chemistry, ICI Pharmaceuticals Group, Wilmington, Delaware 19897, U.S.A. (12 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Based on the possible similarities between LTD4 and its prototypical antagonist FPL-55712, a series of LT antagonists was prepared incorporating a hydroxyacetophenone moiety. They were tested as LTD4 and LTE4 antagonists in vitro using guinea pig trachea (GPT) and selected compounds were tested i.p. against aerosol LTD4 challenge in guinea pigs. FPL-55712 and LY-171883 were used as standards. Structure-activity relationships were evaluated.

L50 ANSWER 10 OF 10 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:179764 SCISEARCH
THE GENUINE ARTICLE: 751JG
TITLE: Design, synthesis and evaluation of beta-amino **hydroxamic** acids as selective tumor necrosis factor-alpha converting enzyme inhibitors.
AUTHOR: Duan J J W (Reprint); Ott G R; King B W; **Maduskuie T P**; Xue C B; Chen L H; Lu Z H; Gilmore J L; Asakawa N; Mercer S E; Xu M Z; Harris C M; Wasserman Z R; Liu R Q; Covington M B; Qian M X; Vaddi K G; Christ D D; Hardman K D; Ribadeneira M D; Newton R C; Trzaskos J M; Decicco C P
CORPORATE SOURCE: Bristol Myers Squibb Co, Pharmaceut Res Inst, Discovery Chem, Princeton, NJ 08543 USA
COUNTRY OF AUTHOR: USA
SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (SEP 2003) Vol. 226, Part 2, pp. U38-U38. MA 201-MEDI.
ISSN: 0065-7727.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 5 Mar 2004
Last Updated on STN: 5 Mar 2004
ED Entered STN: 5 Mar 2004
Last Updated on STN: 5 Mar 2004

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 08:37:18 ON 13 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

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=> d his ful

     (FILE 'HOME' ENTERED AT 10:09:25 ON 11 OCT 2005)

     FILE 'ZCAPLUS' ENTERED AT 10:09:33 ON 11 OCT 2005
               E US2003-632197/APPS

     FILE 'HCAPLUS' ENTERED AT 10:09:56 ON 11 OCT 2005
L1             1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
               SAVE TEMP L1 HOF197HCAAPP/A

     FILE 'STNGUIDE' ENTERED AT 10:10:14 ON 11 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 10:10:27 ON 11 OCT 2005
               D IBIB ED AB IND

     FILE 'STNGUIDE' ENTERED AT 10:10:28 ON 11 OCT 2005

     FILE 'WPIX' ENTERED AT 10:12:02 ON 11 OCT 2005
L2             1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
               SAVE TEMP L2 HOF197WPIAPP/A
               D IALL CMC

     FILE 'STNGUIDE' ENTERED AT 10:12:38 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:13:30 ON 11 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 10:13:33 ON 11 OCT 2005
L3             TRA L1 1- RN :       98 TERMS

     FILE 'REGISTRY' ENTERED AT 10:13:37 ON 11 OCT 2005
L4            98 SEA ABB=ON  PLU=ON  L3
               SAVE TEMP L4 HOF197REGAPP/A

     FILE 'STNGUIDE' ENTERED AT 10:13:48 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:13:58 ON 11 OCT 2005
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 10:14:29 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:29:04 ON 11 OCT 2005
L5            53 SEA ABB=ON  PLU=ON  L4 AND (C6 (S) NC5)/ESS
L6            52 SEA ABB=ON  PLU=ON  L5 AND NRS>1
L7            77 SEA ABB=ON  PLU=ON  L4 AND (C6 (S) C6)/ESS

     FILE 'STNGUIDE' ENTERED AT 10:31:00 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:34:31 ON 11 OCT 2005
L8             1 SEA ABB=ON  PLU=ON  QUINOLINE/CN
               D IDE RSD
L9             1 SEA ABB=ON  PLU=ON  NAPHTHALENE/CN
               D IDE RSD

     FILE 'STNGUIDE' ENTERED AT 10:36:18 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:57:24 ON 11 OCT 2005
L10            0 SEA ABB=ON  PLU=ON  L4 AND C6-NC5/ES

     FILE 'STNGUIDE' ENTERED AT 10:57:48 ON 11 OCT 2005
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     FILE 'REGISTRY' ENTERED AT 10:58:10 ON 11 OCT 2005
L11           53 SEA ABB=ON  PLU=ON  NC5-C6/ES AND L4
L12            9 SEA ABB=ON  PLU=ON  C6-C6/ES AND L4
L13           52 SEA ABB=ON  PLU=ON  L11 AND NRS>1
                 D SCAN L12

     FILE 'STNGUIDE' ENTERED AT 10:59:14 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 10:59:58 ON 11 OCT 2005
L14            6 SEA ABB=ON  PLU=ON  L12 NOT L11
L15            0 SEA ABB=ON  PLU=ON  L14 AND SI=0
                 D SCAN L14

     FILE 'STNGUIDE' ENTERED AT 11:01:10 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 11:01:44 ON 11 OCT 2005
L16            4 SEA ABB=ON  PLU=ON  L14 AND (SI/ELS OR BR/ELS)
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 11:02:04 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 11:02:22 ON 11 OCT 2005
L17            2 SEA ABB=ON  PLU=ON  L14 NOT L16
                 D SCAN
L18            1 SEA ABB=ON  PLU=ON  L17 AND N/ELS
                 D SCAN
                 SAVE TEMP L18 HOF197RCLNAP/A
L19           45 SEA ABB=ON  PLU=ON  L4 NOT (L13 OR L18)
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 11:04:52 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 11:09:02 ON 11 OCT 2005
L20            1 SEA ABB=ON  PLU=ON  L11 NOT L13
                 D SCAN
                 SAVE TEMP L13 HOF197RCLQUI/A

     FILE 'STNGUIDE' ENTERED AT 11:10:23 ON 11 OCT 2005
                 D SAVED

     FILE 'REGISTRY' ENTERED AT 11:11:13 ON 11 OCT 2005
                 D SCAN L13
                 D SCAN L18

     FILE 'STNGUIDE' ENTERED AT 11:11:38 ON 11 OCT 2005


     FILE HOME

     FILE ZCAPLUS
```

strictly prohibited.

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE HCAPLUS

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

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FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

FILE WPIX
FILE LAST UPDATED: 6 OCT 2005 <20051006/UP>
MOST RECENT DERWENT UPDATE: 200564 <200564/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://thomsonderwent.com/coverage/latestupdates/ <<<

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FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3
DICTIONARY FILE UPDATES: 10 OCT 2005 HIGHEST RN 864908-12-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
*
* The CA roles and document type information have been removed from *
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* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

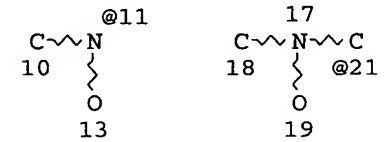
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

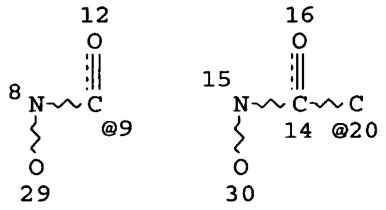
=> => log y

STN INTERNATIONAL LOGOFF AT 11:29:21 ON 11 OCT 2005

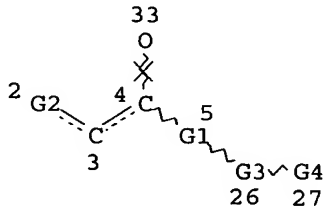
=> d que stat l59
L57 STR



Cb @22 Cb @23 Hy @24 Hy @25 A @28



Cb @31 Hy @32



VAR G1=22/23/24/25
VAR G2=9/11/20/21
REP G3=(2-20) 28
VAR G4=31/32

```
NODE ATTRIBUTES:
NSPEC    IS RC      AT   3
NSPEC    IS RC      AT   4
NSPEC    IS RC      AT  20
NSPEC    IS RC      AT  21
NSPEC    IS RC      AT  28
NSPEC    IS RC      AT  33
CONNECT IS E2  RC AT   8
CONNECT IS E1  RC AT  13
CONNECT IS E2  RC AT  15
CONNECT IS E1  RC AT  19
CONNECT IS M2  RC AT  22
CONNECT IS M2  RC AT  23
CONNECT IS M2  RC AT  24
CONNECT IS M2  RC AT  25
DEFAULT MLEVEL IS ATOM
GGCAT    IS MCY  UNS  AT  22
GGCAT    IS PCY  UNS  AT  23
GGCAT    IS MCY  UNS  AT  24
GGCAT    IS MCY  UNS  AT  25
DEFAULT ECLEVEL IS LIMITED
ECOUNT   IS E6 C  AT  22
ECOUNT   IS E10 C  AT  23
ECOUNT   IS E5 C  E1 N  AT  24
ECOUNT   IS E4 C  E2 N  AT  25
ECOUNT   IS M3-X13 C  AT  31
ECOUNT   IS M1-X13 C  AT  32

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
L59           57 SEA FILE=REGISTRY SSS FUL L57

100.0% PROCESSED   65451 ITERATIONS                          57 ANSWERS
SEARCH TIME: 00.00.01


=> d que nos l63
L57              STR
L62            2 SEA FILE=BEILSTEIN SSS FUL L57
L63            1 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L62 NOT RN/FA


=> d his l66

     (FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS'
     ENTERED AT 16:23:16 ON 11 OCT 2005)
L66           26 DUP REM L65 (8 DUPLICATES REMOVED)
                 SAVE TEMP L66 HOF197MULS1/A

     FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005
```

FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005

FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005

FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005

FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005

FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005

FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:27:46 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:27:56 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:28:54 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:29:02 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:29:44 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:29:50 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:06 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:30:08 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:18 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:30:20 ON 11 OCT 2005

FILE 'CHEMCATS' ENTERED AT 16:30:31 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:31:09 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:31:25 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:31:29 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:32:00 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:32:01 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:32:11 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:32:13 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:33:02 ON 11 OCT 2005

```
=> d que nos l66
L57             STR
L59           57 SEA FILE=REGISTRY SSS FUL L57
L65           34 SEA L59
L66           26 DUP REM L65 (8 DUPLICATES REMOVED)


=> d l64
L64         ANALYZE L59 1- LC :        7 TERMS

TERM #    # OCC   # DOC   % DOC LC
------ ------- ------ ------ ---------------
     1       56     56  98.25 CA
     2       56     56  98.25 CAPLUS
     3       52     52  91.23 USPATFULL
     4       46     46  80.70 TOXCENTER
     5        1      1   1.75 BEILSTEIN
     6        1      1   1.75 CHEMCATS
     7        1      1   1.75 USPAT2
*********  END OF L64***


=> d his ful

     (FILE 'HOME' ENTERED AT 14:05:26 ON 11 OCT 2005)

     FILE 'HCAPLUS' ENTERED AT 14:05:40 ON 11 OCT 2005
               ACT HOF197HCAAPP/A
               ---------
L1            1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
               ---------

     FILE 'STNGUIDE' ENTERED AT 14:05:56 ON 11 OCT 2005

     FILE 'WPIX' ENTERED AT 14:06:04 ON 11 OCT 2005
               ACT HOF197WPIAPP/A
               ---------
L2            1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
               ---------

     FILE 'REGISTRY' ENTERED AT 14:06:24 ON 11 OCT 2005
               ACT HOF197RCLNAP/A
               ---------
L3   (         1)SEA ABB=ON  PLU=ON  US2003-632197/APPS
L4              SEL PLU=ON  L3 1- RN :       98 TERMS
L5   (        98)SEA ABB=ON  PLU=ON  L4
L6   (        53)SEA ABB=ON  PLU=ON  NC5-C6/ES AND L5
L7   (         9)SEA ABB=ON  PLU=ON  C6-C6/ES AND L5
L8   (         6)SEA ABB=ON  PLU=ON  L7 NOT L6
L9   (         4)SEA ABB=ON  PLU=ON  L8 AND (SI/ELS OR BR/ELS)
L10  (         2)SEA ABB=ON  PLU=ON  L8 NOT L9
L11            1 SEA ABB=ON  PLU=ON  L10 AND N/ELS
               ---------
               ACT HOF197RCLQUI/A
               ---------
L12  (         1)SEA ABB=ON  PLU=ON  US2003-632197/APPS
L13             SEL PLU=ON  L12 1- RN :       98 TERMS
L14  (        98)SEA ABB=ON  PLU=ON  L13
L15  (        53)SEA ABB=ON  PLU=ON  NC5-C6/ES AND L14
```

```
L16          52 SEA ABB=ON  PLU=ON  L15 AND NRS>1
               ---------
L17          46 SEA ABB=ON  PLU=ON  L16 AND N>1
L18           6 SEA ABB=ON  PLU=ON  L16 NOT L17
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:07:38 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 14:08:14 ON 11 OCT 2005
                SAVE TEMP L17 HOF197RCLQ2/A

     FILE 'STNGUIDE' ENTERED AT 14:08:27 ON 11 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 14:08:40 ON 11 OCT 2005
L19             3 SEA ABB=ON  PLU=ON  L16
L20             1 SEA ABB=ON  PLU=ON  L17

     FILE 'STNGUIDE' ENTERED AT 14:08:52 ON 11 OCT 2005
                D SAVED

     FILE 'LREGISTRY' ENTERED AT 14:09:24 ON 11 OCT 2005
L21             STR

     FILE 'REGISTRY' ENTERED AT 14:22:27 ON 11 OCT 2005
L22             5 SEA SSS SAM L21
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:23:06 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:24:52 ON 11 OCT 2005
L23             STR L21

     FILE 'REGISTRY' ENTERED AT 14:35:54 ON 11 OCT 2005
L24             0 SEA SSS SAM L23
L25       1416999 SEA ABB=ON  PLU=ON  (C6 (S) NC5)/ESS
L26       1085117 SEA ABB=ON  PLU=ON  L25 AND N>1
L27             8 SEA SUB=L26 SSS SAM L23
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:37:43 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 14:40:05 ON 11 OCT 2005
L28           355 SEA SUB=L26 SSS FUL L23
                SAVE TEMP L28 HOF197PSET1/A
L29            46 SEA ABB=ON  PLU=ON  L28 AND L17

     FILE 'STNGUIDE' ENTERED AT 14:41:06 ON 11 OCT 2005
                D SAVED

     FILE 'HCAPLUS' ENTERED AT 14:41:40 ON 11 OCT 2005
L30            75 SEA ABB=ON  PLU=ON  L28
L31            54 SEA ABB=ON  PLU=ON  L30 AND (AY<2002 OR PY<2002 OR PRY<2002)

     FILE 'STNGUIDE' ENTERED AT 14:42:43 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 14:43:17 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:43:54 ON 11 OCT 2005
L32             STR L23
```

```
     FILE 'REGISTRY' ENTERED AT 14:45:53 ON 11 OCT 2005
L33           10 SEA SUB=L28 SSS SAM L32
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:46:59 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:48:19 ON 11 OCT 2005
L34              STR L32

     FILE 'REGISTRY' ENTERED AT 14:49:19 ON 11 OCT 2005
L35            6 SEA SUB=L28 SSS SAM L34
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:49:39 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:50:34 ON 11 OCT 2005
L36              STR L34

     FILE 'REGISTRY' ENTERED AT 14:53:22 ON 11 OCT 2005
L37            0 SEA SUB=L28 SSS SAM L36
                 D QUE STAT

     FILE 'STNGUIDE' ENTERED AT 14:53:41 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:54:28 ON 11 OCT 2005
L38              STR L36

     FILE 'REGISTRY' ENTERED AT 14:55:03 ON 11 OCT 2005
L39            0 SEA SUB=L28 SSS SAM L38
                 D QUE STAT

     FILE 'STNGUIDE' ENTERED AT 14:55:18 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 14:56:05 ON 11 OCT 2005
L40           84 SEA SUB=L28 SSS FUL L38
                 SAVE TEMP L40 HOF197RSET1/A
L41           46 SEA ABB=ON  PLU=ON  L40 AND L17
L42           38 SEA ABB=ON  PLU=ON  L40 NOT L17
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:58:08 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 15:02:28 ON 11 OCT 2005
L43              STR L38

     FILE 'REGISTRY' ENTERED AT 15:03:28 ON 11 OCT 2005
L44            0 SEA SUB=L40 SSS SAM L43
L45           71 SEA SUB=L40 SSS FUL L43
                 SAVE TEMP L45 HOF197RSET2/ HOF197RSET2/A
L46           46 SEA ABB=ON  PLU=ON  L45 AND L17
L47           25 SEA ABB=ON  PLU=ON  L45 NOT L17
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 15:05:00 ON 11 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 15:07:09 ON 11 OCT 2005
L48            3 SEA ABB=ON  PLU=ON  L47
                 D IBIB 1-3

     FILE 'STNGUIDE' ENTERED AT 15:07:27 ON 11 OCT 2005
```

```
                D COST

     FILE 'STNGUIDE' ENTERED AT 15:08:35 ON 11 OCT 2005
                D SAVED

     FILE 'LREGISTRY' ENTERED AT 15:10:39 ON 11 OCT 2005
L49             STR L43

     FILE 'STNGUIDE' ENTERED AT 15:14:50 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 15:14:57 ON 11 OCT 2005
L50           2 SEA SSS SAM L49
                D SCAN

     FILE 'LREGISTRY' ENTERED AT 15:16:55 ON 11 OCT 2005
L51             STR L49

     FILE 'REGISTRY' ENTERED AT 15:17:39 ON 11 OCT 2005
L52           4 SEA SSS SAM L51
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 15:17:54 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 15:21:38 ON 11 OCT 2005
L53             STR L51

     FILE 'REGISTRY' ENTERED AT 15:22:20 ON 11 OCT 2005
L54           0 SEA SSS SAM L53
                D QUE STAT

     FILE 'STNGUIDE' ENTERED AT 15:22:53 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 15:23:52 ON 11 OCT 2005
L55             STR L53

     FILE 'REGISTRY' ENTERED AT 15:24:44 ON 11 OCT 2005
L56           0 SEA SSS SAM L55
                D QUE STAT

     FILE 'STNGUIDE' ENTERED AT 15:24:54 ON 11 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 15:29:55 ON 11 OCT 2005
L57             STR L55

     FILE 'REGISTRY' ENTERED AT 15:30:49 ON 11 OCT 2005
L58           0 SEA SSS SAM L57
                D QUE STAT

     FILE 'STNGUIDE' ENTERED AT 15:31:00 ON 11 OCT 2005

     FILE 'REGISTRY' ENTERED AT 15:35:36 ON 11 OCT 2005
L59          57 SEA SSS FUL L57
                SAVE TEMP L59 HOF197PSET2/A
L60          46 SEA ABB=ON  PLU=ON  L59 AND L17
L61          11 SEA ABB=ON  PLU=ON  L59 NOT L17
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 15:37:08 ON 11 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 15:42:21 ON 11 OCT 2005
```

```
                D SAVED
                D QUE STAT L59
                D QUE STAT L59

      FILE 'REGISTRY' ENTERED AT 16:15:19 ON 11 OCT 2005
                D SCAN L47

      FILE 'STNGUIDE' ENTERED AT 16:15:44 ON 11 OCT 2005
                D SAVED

      FILE 'BEILSTEIN' ENTERED AT 16:19:14 ON 11 OCT 2005
                D QUE L59
L62               2 SEA SSS FUL L57
L63               1 SEA ABB=ON  PLU=ON  L62 NOT RN/FA
                  SAVE TEMP L63 HOF197BEI1/A

      FILE 'MARPAT' ENTERED AT 16:21:21 ON 11 OCT 2005

      FILE 'STNGUIDE' ENTERED AT 16:21:53 ON 11 OCT 2005

      FILE 'REGISTRY' ENTERED AT 16:22:05 ON 11 OCT 2005
L64               ANALYZE PLU=ON  L59 1- LC :       7 TERMS
                  D

      FILE 'STNGUIDE' ENTERED AT 16:22:38 ON 11 OCT 2005

      FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, BEILSTEIN, CHEMCATS' ENTERED
      AT 16:23:16 ON 11 OCT 2005
L65              34 SEA ABB=ON  PLU=ON  L59
L66              26 DUP REM L65 (8 DUPLICATES REMOVED)
                        ANSWERS '1-10' FROM FILE HCAPLUS
                        ANSWERS '11-22' FROM FILE USPATFULL
                        ANSWER '23' FROM FILE BEILSTEIN
                        ANSWERS '24-26' FROM FILE CHEMCATS
                   SAVE TEMP L66 HOF197MULS1/A
                   D SAVED

      FILE 'STNGUIDE' ENTERED AT 16:24:51 ON 11 OCT 2005

      FILE 'STNGUIDE' ENTERED AT 16:25:23 ON 11 OCT 2005

      FILE 'LREGISTRY' ENTERED AT 16:25:43 ON 11 OCT 2005

      FILE 'REGISTRY' ENTERED AT 16:25:45 ON 11 OCT 2005

      FILE 'ZCAPLUS' ENTERED AT 16:25:48 ON 11 OCT 2005

      FILE 'HCAPLUS' ENTERED AT 16:25:51 ON 11 OCT 2005

      FILE 'USPATFULL' ENTERED AT 16:25:58 ON 11 OCT 2005

      FILE 'USPAT2' ENTERED AT 16:26:02 ON 11 OCT 2005

      FILE 'TOXCENTER' ENTERED AT 16:26:06 ON 11 OCT 2005

      FILE 'BEILSTEIN' ENTERED AT 16:26:11 ON 11 OCT 2005

      FILE 'CHEMCATS' ENTERED AT 16:26:16 ON 11 OCT 2005

      FILE 'STNGUIDE' ENTERED AT 16:26:18 ON 11 OCT 2005
```

D QUE STAT L59
D QUE NOS L66
D L64

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FILE 'STNGUIDE' ENTERED AT 16:27:56 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:28:54 ON 11 OCT 2005
D L66 IBIB ED AB IND HITSTR RETABLE 1-10

FILE 'STNGUIDE' ENTERED AT 16:29:02 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:29:44 ON 11 OCT 2005
D IBIB AB HITSTR L66 11-22

FILE 'STNGUIDE' ENTERED AT 16:29:50 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:06 ON 11 OCT 2005
D L66 IDE 23

FILE 'STNGUIDE' ENTERED AT 16:30:08 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:30:18 ON 11 OCT 2005
D RX L66 23

FILE 'STNGUIDE' ENTERED AT 16:30:20 ON 11 OCT 2005

FILE 'CHEMCATS' ENTERED AT 16:30:31 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:31:09 ON 11 OCT 2005

FILE 'HCAPLUS, USPATFULL, BEILSTEIN, CHEMCATS' ENTERED AT 16:31:25 ON 11 OCT 2005
D IALL L66 24-26

FILE 'STNGUIDE' ENTERED AT 16:31:29 ON 11 OCT 2005
D QUE NOS L63

FILE 'BEILSTEIN' ENTERED AT 16:32:00 ON 11 OCT 2005
D IDE L63

FILE 'STNGUIDE' ENTERED AT 16:32:01 ON 11 OCT 2005

FILE 'BEILSTEIN' ENTERED AT 16:32:11 ON 11 OCT 2005
D L63 RX

FILE 'STNGUIDE' ENTERED AT 16:32:13 ON 11 OCT 2005

FILE 'STNGUIDE' ENTERED AT 16:33:02 ON 11 OCT 2005
D QUE STAT L59
D QUE NOS L63
D QUE NOS L66
D L64

FILE HOME

FILE HCAPLUS

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

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FILE LAST UPDATED: 6 OCT 2005 <20051006/UP>
MOST RECENT DERWENT UPDATE: 200564 <200564/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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FILE LREGISTRY
LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE BEILSTEIN
FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON JUNE 29, 2005

FILE COVERS 1771 TO 2005.
FILE CONTAINS 9,271,550 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****
NEW

*** PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**
*** NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

FILE MARPAT
FILE CONTENT: 1988-PRESENT (VOL 143 ISS 15)(20051007/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 6916824 12 JUL 2005
DE 10359831 14 JUL 2005
EP 1550665 06 JUL 2005
JP 2005183717 07 JUL 2005
WO 2005079855 01 SEP 2005

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 6 Oct 2005 (20051006/PD)
FILE LAST UPDATED: 6 Oct 2005 (20051006/ED)
HIGHEST GRANTED PATENT NUMBER: US6952836
HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461
CA INDEXING IS CURRENT THROUGH 6 Oct 2005 (20051006/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 6 Oct 2005 (20051006/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 11 Oct 2005 (20051011/PD)
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)
HIGHEST GRANTED PATENT NUMBER: US2005054189

HIGHEST APPLICATION PUBLICATION NUMBER: US2005222704
CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

FILE TOXCENTER

FILE COVERS 1907 TO 11 Oct 2005 (20051011/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

FILE CHEMCATS

FILE LAST UPDATED 08 OCTOBER 2005 (20051008/UP)

For details on recent updates in CHEMCATS, enter NEWS FILE at an arrow prompt. For the list of suppliers currently in the file, enter HELP SPA, HELP SPBC, HELP SPDH, HELP SPIN, HELP SPOP, and HELP SPQZ. For the list of current catalogs, enter HELP CTA, HELP CTBC, HELP CTDH, HELP CTIN, HELP CTOP, and HELP CTQZ.

This database is provided on an "as is" basis. Please consult the suppliers for current information regarding pricing, regional availability, available quantities, purities, etc. THERE ARE NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. ACS is not liable for any loss of profit, goodwill or any other damages arising out of the use of this database.

CHEMCATS now contains more than 8 million records. See HELP CONTENT and NEWS FILE for details.

FILE ZCAPLUS

FILE COVERS 1907 - 11 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 10 Oct 2005 (20051010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> => d his l11

     (FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005)
L11            2 DUP REM L10 (1 DUPLICATE REMOVED)

=> d que l11
L1   (         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2003-632197/APPS
L2               SEL  PLU=ON  L1 1- RN :       98 TERMS
L3   (        98)SEA FILE=REGISTRY ABB=ON  PLU=ON  L2
L4   (        53)SEA FILE=REGISTRY ABB=ON  PLU=ON  NC5-C6/ES AND L3
L5   (         9)SEA FILE=REGISTRY ABB=ON  PLU=ON  C6-C6/ES AND L3
L6   (         6)SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 NOT L4
L7   (         4)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 AND (SI/ELS OR BR/ELS)
L8   (         2)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L7
L9             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND N/ELS
L10            3 SEA L9
L11            2 DUP REM L10 (1 DUPLICATE REMOVED)


=> d his ful

     (FILE 'HOME' ENTERED AT 14:42:08 ON 12 OCT 2005)

     FILE 'REGISTRY' ENTERED AT 14:42:17 ON 12 OCT 2005
               ACT HOF197RCLNAP/A
               ---------
L1   (         1)SEA ABB=ON  PLU=ON  US2003-632197/APPS
L2               SEL PLU=ON  L1 1- RN :       98 TERMS
L3   (        98)SEA ABB=ON  PLU=ON  L2
L4   (        53)SEA ABB=ON  PLU=ON  NC5-C6/ES AND L3
L5   (         9)SEA ABB=ON  PLU=ON  C6-C6/ES AND L3
L6   (         6)SEA ABB=ON  PLU=ON  L5 NOT L4
L7   (         4)SEA ABB=ON  PLU=ON  L6 AND (SI/ELS OR BR/ELS)
L8   (         2)SEA ABB=ON  PLU=ON  L6 NOT L7
L9             1 SEA ABB=ON  PLU=ON  L8 AND N/ELS
               ---------
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 14:43:11 ON 12 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 14:43:44 ON 12 OCT 2005
```

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     FILE 'ZCAPLUS' ENTERED AT 14:43:47 ON 12 OCT 2005

     FILE 'LREGISTRY' ENTERED AT 14:43:50 ON 12 OCT 2005

     FILE 'REGISTRY' ENTERED AT 14:43:52 ON 12 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 14:43:54 ON 12 OCT 2005
               D QUE L9

     FILE 'REGISTRY' ENTERED AT 14:44:08 ON 12 OCT 2005
               D IDE L9

     FILE 'STNGUIDE' ENTERED AT 14:44:09 ON 12 OCT 2005

     FILE 'HCAPLUS, TOXCENTER, USPATFULL' ENTERED AT 14:44:48 ON 12 OCT 2005
L10             3 SEA ABB=ON  PLU=ON  L9
L11             2 DUP REM L10 (1 DUPLICATE REMOVED)
                      ANSWER '1' FROM FILE HCAPLUS
                      ANSWER '2' FROM FILE USPATFULL
                  SAVE TEMP L11 HOF197MULS2/A
                  D SAVED

     FILE 'STNGUIDE' ENTERED AT 14:45:55 ON 12 OCT 2005
               D QUE L11

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 14:46:26 ON 12 OCT 2005
               D IBIB ED AB HITSTR L11 1

     FILE 'STNGUIDE' ENTERED AT 14:46:27 ON 12 OCT 2005

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 14:46:53 ON 12 OCT 2005
               D IBIB AB HITSTR L11 2

     FILE 'STNGUIDE' ENTERED AT 14:46:53 ON 12 OCT 2005

     FILE 'WPIX' ENTERED AT 14:47:36 ON 12 OCT 2005
               ACT HOF197WPIAPP/A
              ---------
L12             1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
               ---------
                  SELECT L12 1- DCN
L13             1 SEA ABB=ON  PLU=ON  (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR
                  RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR
                  RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR
                  RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR
                  RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR
                  RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR
                  RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR
                  0125-21302/DCN OR 0125-21303/DCN OR 0125-21304/DCN OR 0125-2130
                  5/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR
                  0125-21309/DCN OR 0125-21310/DCN OR 0125-21311/DCN OR 0125-2131
                  2/DCN OR 0125-21313/DCN OR 0125-21314/DCN)

     FILE 'STNGUIDE' ENTERED AT 14:48:23 ON 12 OCT 2005

     FILE 'WPIX' ENTERED AT 15:00:23 ON 12 OCT 2005
               D CMC L12

     FILE 'STNGUIDE' ENTERED AT 15:00:26 ON 12 OCT 2005
```

```
     FILE 'WPIX' ENTERED AT 15:04:55 ON 12 OCT 2005
L14       27282 SEA ABB=ON  PLU=ON  ((D621 OR D622)(P) (G011 OR G012 OR G013
                OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1,M2,M3,M
                4,M5,M6

     FILE 'STNGUIDE' ENTERED AT 15:05:31 ON 12 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 15:05:58 ON 12 OCT 2005
L15       32505 SEA ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L16             QUE ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?

     FILE 'STNGUIDE' ENTERED AT 15:06:12 ON 12 OCT 2005

     FILE 'WPIX' ENTERED AT 15:06:19 ON 12 OCT 2005
L17         253 SEA ABB=ON  PLU=ON  (L13 OR L14) AND (?HYDANTOI?/BIX OR
                ?HYDROXAM?/BIX)

     FILE 'STNGUIDE' ENTERED AT 15:07:06 ON 12 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 15:10:17 ON 12 OCT 2005
L18             QUE ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? OR
                (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A)?NECR
                O?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS?))

     FILE 'WPIX' ENTERED AT 15:10:39 ON 12 OCT 2005
L19          48 SEA ABB=ON  PLU=ON  L17 AND (MMP/BIX OR (?MATRIX?/BIX(2A)(?META
                LLOPROT?/BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR
                ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR
                (?ALPHA?/BIX(2A)(?CONVERT?/BIX OR ?CONVERS?/BIX)))
L20         168 SEA ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (7A)
                (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR (?METALLO/BI
                X(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(
                2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A)(?CONVERT?/BIX
                OR ?CONVERS?/BIX)))
L21          19 SEA ABB=ON  PLU=ON  L19 AND L20
L22           0 SEA ABB=ON  PLU=ON  L12 AND L21
L23         328 SEA ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L)
                (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR (?METALLO/BI
                X(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(
                2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A)(?CONVERT?/BIX
                OR ?CONVERS?/BIX)))
L24           1 SEA ABB=ON  PLU=ON  L23 AND L12
L25          40 SEA ABB=ON  PLU=ON  (L13 OR L14) AND L23

     FILE 'STNGUIDE' ENTERED AT 15:15:33 ON 12 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 15:18:49 ON 12 OCT 2005
L26             QUE ABB=ON  PLU=ON  ?INHIBIT? OR ?REPRESS? OR ?SUPRESS? OR
                ?DISRUPT? OR ?INTERRUPT? OR ?ANTAGON? OR ?PROHIBIT? OR
                ?PREVENT? OR ?IMPED? OR ?REDUC? OR ?DEPRESS? OR ?BLOCK? OR
                STOP? OR ?RETARD? OR SLOW?

     FILE 'WPIX' ENTERED AT 15:19:03 ON 12 OCT 2005
L27        3929 SEA ABB=ON  PLU=ON  (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?
                /BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/B
                IX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX
                (2A)(?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A) (?INHIBIT?/BIX OR
                ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/BIX OR ?INTERRUPT?/
                BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR ?PREVENT?/BIX OR
                ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX OR ?BLOCK?/BIX OR
```

```
                STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)
L28          304 SEA ABB=ON  PLU=ON  L27 (L) (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX)

L29           38 SEA ABB=ON  PLU=ON  L25 AND L28
                D TRI 1-3
L30           33 SEA ABB=ON  PLU=ON  L29 AND (AY<2003 OR PY<2003 OR PRY<2003)
                SAVE TEMP L29 HOF197WPIP/A

     FILE 'MEDLINE' ENTERED AT 15:58:41 ON 12 OCT 2005
L31        20358 SEA ABB=ON  PLU=ON  L18 (5A) L26
L32          501 SEA ABB=ON  PLU=ON  L16 (10A) L16
                E HYDANTOINS/CT
                E E43+ALL
L33        15228 SEA ABB=ON  PLU=ON  HYDANTOINS+PFT,NT/CT
L34          485 SEA ABB=ON  PLU=ON  L33 (L) AA
L35           38 SEA ABB=ON  PLU=ON  L32 AND L34
                D TRI 1-3

     FILE 'STNGUIDE' ENTERED AT 16:00:41 ON 12 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 16:02:19 ON 12 OCT 2005
L36             QUE ABB=ON  PLU=ON  ?QUINOLIN?
L37             QUE ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? OR
                ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? OR
                ?PYRIMIDIN? OR ?BENZENE?

     FILE 'STNGUIDE' ENTERED AT 16:02:37 ON 12 OCT 2005

     FILE 'MEDLINE' ENTERED AT 16:02:40 ON 12 OCT 2005
L38           4627 SEA ABB=ON  PLU=ON  L16 (L) (L36 OR L37)
L39             38 SEA ABB=ON  PLU=ON  L35 AND L38
                SAVE TEMP L39 HOF197MEDP/A

     FILE 'STNGUIDE' ENTERED AT 16:03:31 ON 12 OCT 2005
                D SAVED
                D QUE L11


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   11 OCT 2005  HIGHEST RN 865062-68-6
     DICTIONARY FILE UPDATES:  11 OCT 2005  HIGHEST RN 865062-68-6

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
```

*
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*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 7, 2005 (20051007/UP).

FILE HCAPLUS

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE ZCAPLUS

FILE COVERS 1907 - 12 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE LREGISTRY
LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE TOXCENTER

FILE COVERS 1907 TO 11 Oct 2005 (20051011/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 11 Oct 2005 (20051011/PD)
FILE LAST UPDATED: 11 Oct 2005 (20051011/ED)
HIGHEST GRANTED PATENT NUMBER: US6954941
HIGHEST APPLICATION PUBLICATION NUMBER: US2005223461
CA INDEXING IS CURRENT THROUGH 11 Oct 2005 (20051011/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Oct 2005 (20051011/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE WPIX
FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>
MOST RECENT DERWENT UPDATE: 200565 <200565/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev
FOR DETAILS. <<<

FILE MEDLINE
FILE LAST UPDATED: 11 OCT 2005 (20051011/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> => d que l20
L11 (1) SEA FILE=WPIX ABB=ON PLU=ON (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR 0125-21302/DCN OR 0125-21303/DCN OR 0125-21304/DCN OR 0125-21305/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR 0125-21309/DCN OR 0125-21310/DCN OR 0125-21311/DCN OR 0125-21312/DCN OR 0125-21313/DCN OR 0125-21314/DCN)
L12 (27282) SEA FILE=WPIX ABB=ON PLU=ON ((D621 OR D622)(P) (G011 OR G012 OR G013 OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1,M2,M3,M4,M5,M6
L13 (328) SEA FILE=WPIX ABB=ON PLU=ON (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L) (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A)(?CONVERT?/BIX OR ?CONVERS?/BIX)))
L14 (40) SEA FILE=WPIX ABB=ON PLU=ON (L11 OR L12) AND L13
L15 (3929) SEA FILE=WPIX ABB=ON PLU=ON (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR

```
                ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR
                (?ALPHA?/BIX(2A)(?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A)
                (?INHIBIT?/BIX OR ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/B
                IX OR ?INTERRUPT?/BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR
                ?PREVENT?/BIX OR ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX
                OR ?BLOCK?/BIX OR STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)
L16 (       304)SEA FILE=WPIX ABB=ON  PLU=ON  L15 (L) (?HYDANTOI?/BIX OR
                ?HYDROXAM?/BIX)
L17          38 SEA FILE=WPIX ABB=ON  PLU=ON  L14 AND L16
L19         196 SEA FILE=WPIX ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX
                ) (L) (?QUINOLIN?/BIX)
L20          14 SEA FILE=WPIX ABB=ON  PLU=ON  L17 AND L19


=> d que l31
L1               QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L6               QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7               QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                 R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                 R ?PYRIMIDIN? OR ?BENZENE?
L21              QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                 R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                 2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                 ?))
L23         15230 SEA FILE=MEDLINE ABB=ON  PLU=ON  HYDANTOINS+PFT,NT/CT
L24           485 SEA FILE=MEDLINE ABB=ON  PLU=ON  L23 (L) AA
L25             3 SEA FILE=MEDLINE ABB=ON  PLU=ON  L24 AND L21
L26           367 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (L) L21
L27           970 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (10A) (L6 OR L7)
L28            34 SEA FILE=MEDLINE ABB=ON  PLU=ON  L26 AND L27
L29            14 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 (7A) L6
L30             4 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND L29
L31             7 SEA FILE=MEDLINE ABB=ON  PLU=ON  L25 OR L30


=> d que l39
L1               QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L6               QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7               QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                 R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                 R ?PYRIMIDIN? OR ?BENZENE?
L21              QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                 R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                 2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                 ?))
L32         50409 SEA FILE=EMBASE ABB=ON  PLU=ON  "HYDANTOIN DERIVATIVE"+PFT,NT/C
                 T
L33           187 SEA FILE=EMBASE ABB=ON  PLU=ON  L32 AND L21
L36           391 SEA FILE=EMBASE ABB=ON  PLU=ON  L1 (L) L21
L37            17 SEA FILE=EMBASE ABB=ON  PLU=ON  L33 AND L36
L38            11 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 AND (L6 OR L7)
L39            17 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 OR L38


=> d his l47

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'
     ENTERED AT 08:16:50 ON 13 OCT 2005)
L47            53 DUP REM L46 (21 DUPLICATES REMOVED)
```

```
=> d que l47
L1              QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L6              QUE  ABB=ON  PLU=ON  ?QUINOLIN?
L7              QUE  ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? O
                R ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? O
                R ?PYRIMIDIN? OR ?BENZENE?
L21             QUE  ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? O
                R (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(
                2A)?NECRO?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS
                ?))
L40          6407 SEA L1 (7A) (L6 OR L7)
L41         20700 SEA L1/TI,IT,CC,CT,ST,STP
L42          4900 SEA L40 AND L41
L43          1538 SEA L1 (L) L21
L44            87 SEA L42 AND L43
L45        269429 SEA L21/TI,IT,CC,CT,ST,STP
L46            74 SEA L44 AND L45
L47            53 DUP REM L46 (21 DUPLICATES REMOVED)


=> d his l50

     (FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA,
     CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT
     08:28:53 ON 13 OCT 2005)
L50            10 DUP REM L49 (3 DUPLICATES REMOVED)

=> d que l50
L1              QUE  ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L48           147 SEA MADUSKUIE, T?/AU
L49            13 SEA L48 AND L1
L50            10 DUP REM L49 (3 DUPLICATES REMOVED)


=> d his ful

     (FILE 'HOME' ENTERED AT 07:50:52 ON 13 OCT 2005)

     FILE 'MEDLINE' ENTERED AT 07:51:03 ON 13 OCT 2005
                ACT HOF197MEDP/A
               ---------
L1              QUE ABB=ON  PLU=ON  ?HYDANTOI? OR ?HYDROXAM?
L2   (         501)SEA ABB=ON  PLU=ON  L1 (10A) L1
L3   (       15228)SEA ABB=ON  PLU=ON  HYDANTOINS+PFT,NT/CT
L4   (         485)SEA ABB=ON  PLU=ON  L3 (L) AA
L5   (          38)SEA ABB=ON  PLU=ON  L2 AND L4
L6              QUE ABB=ON  PLU=ON  ?QUINOLIN?
L7              QUE ABB=ON  PLU=ON  ?PHENYL? OR ?BENZYL? OR ?NAPHTHYL? OR
                ?NAPHTHENYL? OR ?PYRIDYL? OR ?PYRIDIN? OR ?PYRIMIDYL? OR
                ?PYRIMIDIN? OR ?BENZENE?
L8   (        4627)SEA ABB=ON  PLU=ON  L1 (L) (L6 OR L7)
L9              38 SEA ABB=ON  PLU=ON  L5 AND L8
               ---------

     FILE 'STNGUIDE' ENTERED AT 07:51:12 ON 13 OCT 2005

     FILE 'WPIX' ENTERED AT 07:52:15 ON 13 OCT 2005
                ACT HOF197WPIAPP/A
               ---------
L10              1 SEA ABB=ON  PLU=ON  US2003-632197/APPS
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                ACT HOF197WPIP/A
               ---------
L11 (          1)SEA ABB=ON  PLU=ON  (RADLBS/DCN OR RADLCX/DCN OR RADLCZ/DCN OR
                  RADLD1/DCN OR RADLD3/DCN OR RADLD6/DCN OR RADL2W/DCN OR
                  RADL2X/DCN OR RADL2Y/DCN OR RADL2Z/DCN OR RADL3C/DCN OR
                  RADL3E/DCN OR RADL3J/DCN OR RADL3K/DCN OR RADL3W/DCN OR
                  RADL3Y/DCN OR RADL3Z/DCN OR RADL30/DCN OR RADL4D/DCN OR
                  RADL4J/DCN OR RADL40/DCN OR RADL41/DCN OR RADL42/DCN OR
                  RADL47/DCN OR RADL81/DCN OR RADL89/DCN OR 0125-21301/DCN OR
                  0125-21302/DCN OR 0125-21303/DCN OR 0125-21304/DCN OR 0125-2130
                  5/DCN OR 0125-21306/DCN OR 0125-21307/DCN OR 0125-21308/DCN OR
                  0125-21309/DCN OR 0125-21310/DCN OR 0125-21311/DCN OR 0125-2131
                  2/DCN OR 0125-21313/DCN OR 0125-21314/DCN)
L12 (      27282)SEA ABB=ON  PLU=ON  ((D621 OR D622)(P) (G011 OR G012 OR G013
                  OR G014 OR G015 OR G016 OR G221 OR F431 OR F541))/M0,M1,M2,M3,M
                  4,M5,M6
L13 (        328)SEA ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L)
                  (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?/BIX OR (?METALLO/BI
                  X(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/BIX OR ?TUMOUR?/BIX)(
                  2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX(2A)(?CONVERT?/BIX
                  OR ?CONVERS?/BIX)))
L14 (         40)SEA ABB=ON  PLU=ON  (L11 OR L12) AND L13
L15 (       3929)SEA ABB=ON  PLU=ON  (MMP/BIX OR (?MATRIX?/BIX(2A)(?METALLOPROT?
                  /BIX OR (?METALLO/BIX(1W)PROT?/BIX))) OR TNF/BIX OR ((?TUMOR?/B
                  IX OR ?TUMOUR?/BIX)(2A)?NECRO?/BIX) OR TACE/BIX OR (?ALPHA?/BIX
                  (2A)(?CONVERT?/BIX OR ?CONVERS?/BIX))) (7A) (?INHIBIT?/BIX OR
                  ?REPRESS?/BIX OR ?SUPRESS?/BIX OR ?DISRUPT?/BIX OR ?INTERRUPT?/
                  BIX OR ?ANTAGON?/BIX OR ?PROHIBIT?/BIX OR ?PREVENT?/BIX OR
                  ?IMPED?/BIX OR ?REDUC?/BIX OR ?DEPRESS?/BIX OR ?BLOCK?/BIX OR
                  STOP?/BIX OR ?RETARD?/BIX OR SLOW?/BIX)
L16 (        304)SEA ABB=ON  PLU=ON  L15 (L) (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX)

L17           38 SEA ABB=ON  PLU=ON  L14 AND L16
                 ---------
                 D QUE

     FILE 'STNGUIDE' ENTERED AT 07:53:01 ON 13 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 07:56:05 ON 13 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 07:56:21 ON 13 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 07:56:44 ON 13 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 07:56:54 ON 13 OCT 2005
L18              QUE ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? OR
                  (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A)?NECR
                  O?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS?))

     FILE 'STNGUIDE' ENTERED AT 07:57:41 ON 13 OCT 2005
                  D QUE L17

     FILE 'WPIX' ENTERED AT 07:58:07 ON 13 OCT 2005
L19           196 SEA ABB=ON  PLU=ON  (?HYDANTOI?/BIX OR ?HYDROXAM?/BIX) (L)
                  (?QUINOLIN?/BIX)
L20            14 SEA ABB=ON  PLU=ON  L17 AND L19

     FILE 'HCAPLUS' ENTERED AT 08:02:33 ON 13 OCT 2005
L21              QUE ABB=ON  PLU=ON  MMP OR (?MATRIX?(2A)(?METALLOPROT? OR
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```
            (?METALLO(1W)PROT?))) OR TNF OR ((?TUMOR? OR ?TUMOUR?)(2A)?NECR
            O?) OR TACE OR (?ALPHA?(2A)(?CONVERT? OR ?CONVERS?))

     FILE 'STNGUIDE' ENTERED AT 08:02:41 ON 13 OCT 2005

     FILE 'WPIX' ENTERED AT 08:02:47 ON 13 OCT 2005
           D TRI L20 1-14

     FILE 'STNGUIDE' ENTERED AT 08:03:09 ON 13 OCT 2005

     FILE 'WPIX' ENTERED AT 08:04:55 ON 13 OCT 2005
           SAVE TEMP L20 HOF197WPI1/A

     FILE 'STNGUIDE' ENTERED AT 08:05:10 ON 13 OCT 2005
           D SAVED

     FILE 'MEDLINE' ENTERED AT 08:05:34 ON 13 OCT 2005
           D QUE L9
L22          0 SEA ABB=ON  PLU=ON  L9 AND L21
L23      15230 SEA ABB=ON  PLU=ON  HYDANTOINS+PFT,NT/CT
L24        485 SEA ABB=ON  PLU=ON  L23 (L) AA
L25          3 SEA ABB=ON  PLU=ON  L24 AND L21
L26        367 SEA ABB=ON  PLU=ON  L1 (L) L21
L27        970 SEA ABB=ON  PLU=ON  L1 (10A) (L6 OR L7)
L28         34 SEA ABB=ON  PLU=ON  L26 AND L27
L29         14 SEA ABB=ON  PLU=ON  L1 (7A) L6
L30          4 SEA ABB=ON  PLU=ON  L28 AND L29
L31          7 SEA ABB=ON  PLU=ON  L25 OR L30
           D TRI 1-7

     FILE 'STNGUIDE' ENTERED AT 08:08:34 ON 13 OCT 2005

     FILE 'MEDLINE' ENTERED AT 08:09:30 ON 13 OCT 2005
           D KWIC 1-7

     FILE 'STNGUIDE' ENTERED AT 08:09:30 ON 13 OCT 2005

     FILE 'MEDLINE' ENTERED AT 08:09:46 ON 13 OCT 2005
           D TI KWIC 1-7

     FILE 'STNGUIDE' ENTERED AT 08:09:46 ON 13 OCT 2005

     FILE 'STNGUIDE' ENTERED AT 08:09:51 ON 13 OCT 2005

     FILE 'MEDLINE' ENTERED AT 08:10:55 ON 13 OCT 2005
           SAVE TEMP L31 HOF197MED1/A

     FILE 'STNGUIDE' ENTERED AT 08:11:11 ON 13 OCT 2005

     FILE 'EMBASE' ENTERED AT 08:11:14 ON 13 OCT 2005
           E HYDANTOIN/CT
L32      50409 SEA ABB=ON  PLU=ON  "HYDANTOIN DERIVATIVE"+PFT,NT/CT
L33        187 SEA ABB=ON  PLU=ON  L32 AND L21
L34         17 SEA ABB=ON  PLU=ON  L1 (10A) L6
L35          0 SEA ABB=ON  PLU=ON  L33 AND L34
L36        391 SEA ABB=ON  PLU=ON  L1 (L) L21
L37         17 SEA ABB=ON  PLU=ON  L33 AND L36
           D TRI 1-17

     FILE 'STNGUIDE' ENTERED AT 08:13:08 ON 13 OCT 2005
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     FILE 'EMBASE' ENTERED AT 08:14:44 ON 13 OCT 2005
L38           11 SEA ABB=ON  PLU=ON  L37 AND (L6 OR L7)
L39           17 SEA ABB=ON  PLU=ON  L37 OR L38
                 SAVE TEMP L39 HOF197EMB1/A

     FILE 'STNGUIDE' ENTERED AT 08:15:21 ON 13 OCT 2005
                 D SAVED

     FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, CANCERLIT, DRUGU, SCISEARCH'
     ENTERED AT 08:16:50 ON 13 OCT 2005
L40         6407 SEA ABB=ON  PLU=ON  L1 (7A) (L6 OR L7)
L41        20700 SEA ABB=ON  PLU=ON  L1/TI,IT,CC,CT,ST,STP
L42         4900 SEA ABB=ON  PLU=ON  L40 AND L41
L43         1538 SEA ABB=ON  PLU=ON  L1 (L) L21
L44           87 SEA ABB=ON  PLU=ON  L42 AND L43
L45       269429 SEA ABB=ON  PLU=ON  L21/TI,IT,CC,CT,ST,STP
L46           74 SEA ABB=ON  PLU=ON  L44 AND L45
L47           53 DUP REM L46 (21 DUPLICATES REMOVED)
                      ANSWERS '1-19' FROM FILE BIOSIS
                      ANSWERS '20-42' FROM FILE PASCAL
                      ANSWER '43' FROM FILE CANCERLIT
                      ANSWERS '44-45' FROM FILE DRUGU
                      ANSWERS '46-53' FROM FILE SCISEARCH
                 SAVE TEMP L47 HOF197MULT1/A
                 D SAVED

     FILE 'STNGUIDE' ENTERED AT 08:27:37 ON 13 OCT 2005

     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, PASCAL, JICST-EPLUS, CABA,
     CANCERLIT, DRUGU, SCISEARCH, WPIX, CONF, CONFSCI, DISSABS' ENTERED AT
     08:28:53 ON 13 OCT 2005
L48          147 SEA ABB=ON  PLU=ON  MADUSKUIE, T?/AU
L49           13 SEA ABB=ON  PLU=ON  L48 AND L1
L50           10 DUP REM L49 (3 DUPLICATES REMOVED)
                      ANSWERS '1-6' FROM FILE HCAPLUS
                      ANSWER '7' FROM FILE BIOSIS
                      ANSWERS '8-9' FROM FILE DRUGU
                      ANSWER '10' FROM FILE SCISEARCH
                 SAVE TEMP L50 HOF197MULINV/A
                 D SAVED

     FILE 'STNGUIDE' ENTERED AT 08:30:44 ON 13 OCT 2005

     FILE 'HCAPLUS' ENTERED AT 08:31:12 ON 13 OCT 2005

     FILE 'MEDLINE' ENTERED AT 08:31:18 ON 13 OCT 2005

     FILE 'WPIX' ENTERED AT 08:31:28 ON 13 OCT 2005

     FILE 'EMBASE' ENTERED AT 08:31:32 ON 13 OCT 2005

     FILE 'BIOSIS' ENTERED AT 08:31:35 ON 13 OCT 2005

     FILE 'PASCAL' ENTERED AT 08:31:39 ON 13 OCT 2005

     FILE 'JICST-EPLUS' ENTERED AT 08:31:42 ON 13 OCT 2005

     FILE 'CABA' ENTERED AT 08:31:45 ON 13 OCT 2005
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FILE 'CANCERLIT' ENTERED AT 08:31:49 ON 13 OCT 2005

FILE 'DRUGU' ENTERED AT 08:31:53 ON 13 OCT 2005

FILE 'SCISEARCH' ENTERED AT 08:31:58 ON 13 OCT 2005

FILE 'CONF' ENTERED AT 08:32:00 ON 13 OCT 2005

FILE 'CONFSCI' ENTERED AT 08:32:09 ON 13 OCT 2005

FILE 'DISSABS' ENTERED AT 08:32:14 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 08:32:16 ON 13 OCT 2005
D QUE L20
D QUE L31
D QUE L39
D QUE L47

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'
ENTERED AT 08:33:16 ON 13 OCT 2005
L51 85 DUP REM L20 L31 L39 L47 (6 DUPLICATES REMOVED)
ANSWERS '1-14' FROM FILE WPIX
ANSWERS '15-21' FROM FILE MEDLINE
ANSWERS '22-37' FROM FILE EMBASE
ANSWERS '38-53' FROM FILE BIOSIS
ANSWERS '54-75' FROM FILE PASCAL
ANSWER '76' FROM FILE CANCERLIT
ANSWERS '77-78' FROM FILE DRUGU
ANSWERS '79-85' FROM FILE SCISEARCH

FILE 'STNGUIDE' ENTERED AT 08:33:24 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'
ENTERED AT 08:33:45 ON 13 OCT 2005
D IALL ABEQ TECH ABEX

FILE 'STNGUIDE' ENTERED AT 08:33:47 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'
ENTERED AT 08:34:40 ON 13 OCT 2005
D IALL ABEQ TECH ABEX 2-14

FILE 'STNGUIDE' ENTERED AT 08:34:50 ON 13 OCT 2005

FILE 'WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, CANCERLIT, DRUGU, SCISEARCH'
ENTERED AT 08:35:33 ON 13 OCT 2005
D IBIB ED AB HITIND 15-

FILE 'STNGUIDE' ENTERED AT 08:35:54 ON 13 OCT 2005
D QUE L50

FILE 'HCAPLUS, BIOSIS, DRUGU, SCISEARCH' ENTERED AT 08:37:05 ON 13 OCT 2005
D IBIB ED AB L50 1-10

FILE 'STNGUIDE' ENTERED AT 08:37:07 ON 13 OCT 2005

FILE 'STNGUIDE' ENTERED AT 08:37:18 ON 13 OCT 2005
D QUE L20
D QUE L31

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D QUE L39
D QUE L47
D QUE L50

FILE HOME

FILE MEDLINE
 FILE LAST UPDATED: 12 OCT 2005 (20051012/UP). FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available. For details enter HELP
 RLOAD at an arrow promt (=>). See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  7, 2005 (20051007/UP).

FILE WPIX
FILE LAST UPDATED:          11 OCT 2005      <20051011/UP>
MOST RECENT DERWENT UPDATE:     200565        <200565/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
    PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev
    FOR DETAILS. <<<

FILE HCAPLUS

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FILE COVERS 1907 - 13 Oct 2005 VOL 143 ISS 16
FILE LAST UPDATED: 12 Oct 2005 (20051012/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 October 2005 (20051012/ED)

FILE RELOADED: 19 October 2003.

FILE PASCAL
FILE LAST UPDATED: 10 OCT 2005 <20051010/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 12 OCT 2005 (20051012/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE CABA
FILE COVERS 1973 TO 7 Oct 2005 (20051007/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the

MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU
FILE LAST UPDATED: 11 OCT 2005 <20051011/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE SCISEARCH

FILE COVERS 1974 TO 6 Oct 2005 (20051006/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONF
FILE LAST UPDATED: 7 OCT 2005 <20051007/UP>
FILE COVERS 1976 TO DATE.

FILE CONFSCI
FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

FILE DISSABS
FILE COVERS 1861 TO 29 SEP 2005 (20050929/ED)

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